FRAILTY PREVALENCE, ONE-YEAR RISK, AND THE EFFECT OF SMOKING AMONG WOMEN WITH AND WITHOUT HIV INFECTION

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ABSTRACT

Terra Victoria Fatukasi: Frailty prevalence, one-year risk, and the effect of smoking among women with and without HIV infection
(Under the direction of Adaora A. Adimora)

The gap in life expectancy between people with HIV and the general population is diminishing. However, evidence suggests that people with HIV may be experiencing aging-related conditions at earlier ages. The objective of this dissertation was to estimate the prevalence of frailty, a syndrome of physical vulnerability, estimate the one-year risk of frailty, and examine the effect of smoking on the one-year risk of frailty among women with and at risk for HIV. This project used data from the Women's Interagency HIV Study between October 2015 and September 2017. The Fried Frailty Index was used to define frail status as exceeding the threshold for at least three of five frailty components: slowness, weakness, unintentional weight loss, exhaustion, and low physical activity. Among 1,404 women with a median age of 52 years (interquartile range: 47-57), we found that frailty prevalence was 11.5% (15.3% HIV-, 10.1% HIV+). The most common frailty components were low physical activity and exhaustion. The one-year risk of frailty was 6.6% (95% confidence interval: 4.1, 9.1) and similar for women with and without HIV. After adjustment for confounding, current smokers were 1.68 times as likely to become frail compared to non-smokers (95% CI: 0.69, 4.06). Women with high cumulative smoking exposure were 2.72 times as likely to become frail compared to women with low cumulative smoking exposure (95% CI: 0.96, 7.67), and this latter effect appeared to be

more pronounced among women with HIV (adjusted RR = 4.10; 95% CI: 1.22, 13.78). In a low income, predominately black population of women in their mid-fifties with and without HIV infection, the prevalence and risk of frailty is comparable to women in the general population at least 65 years old. Reported smoking exposure is independently associated with increased frailty risk in this population, even over a one-year period of follow-up. These findings demonstrate that modifiable risk factors, such as smoking, could play a crucial role in preventing frailty, especially among people with HIV. Future studies are needed to investigate trends in frailty risk over time and to examine the long-term impacts of smoking on frailty among people with HIV.

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LIST OF ABBREVIATIONS

ART	Antiretroviral Therapy
BMI	Body Mass Index
CD4	Cluster of Differentiation 4
CHS	Cardiovascular Health Study
CI	Confidence Interval
DAG	Directed Acyclic Graph
FFI	Fried Frailty Index
HIV	Human Immunodeficiency Virus
IQR	Interquartile Range
MACS	Multicenter AIDS Cohort Study
mL	Milliliter
mm^3	Millimeter
RD	Risk Difference
RR	Risk Ratio
WIHS	Women's Interagency HIV Study
VL	Viral Load
US	United States

CHAPTER 1. BACKGROUND

Many high-income countries, including the United States (US), have seen a shift in population demographics to older ages[1, 2]. Between 1970 and 2015, US life expectancy at birth increased from 70.8 years to 78.8 years[3]. According to the Census Bureau, in 1970, 10% (20 million) of the US population was at least 65 years old[4]. The most recent census in 2010 estimated this figure to be 13% (40 million), but it is projected to be over 20% by 2030 (73 million)[5]. As early as 2035, older adults are projected to outnumber children for the first time in US history[5]. One major driving factor for these changes over time has been declining mortality in late-life from leading causes of death, including cardiovascular disease and cancer[6].

Despite these strides, certain populations still demonstrate marked disparities in life expectancy and mortality[5, 7, 8]. For example, the life expectancy for black non-Hispanics was 75.1 years in 2015[7]. Between 2001 and 2014, the gap in life expectancy between the poorest 1% and richest 1% of individuals was 15 years for men and 10 years for women[9]. During this same period, life expectancy increased by three years for those in the highest quartile of the income distribution, while it remained the same for those in the lowest quartile[9]. Social and structural factors play a critical role in shaping patterns of healthcare access and health-related behaviors among these populations[10].

The life expectancy for people with HIV has rapidly improved over recent years due to the increased effectiveness and use of antiretroviral therapy (ART)[8, 11]. One recent study estimated that 20-year-olds on ART can expect to live into their early 70s[8]. There are currently over 1.2 million adults and adolescents living with HIV infection in the US[12]. In 2014, 45% of people with HIV in the US were aged 50 and older[13]. This is projected to increase to more than 50% by 2020[14-16]. Even with advancements in treatment, there are still disparate outcomes in life expectancy and mortality for people with HIV compared to the general population[8].

Earlier in the HIV/AIDS epidemic, differences in life expectancy between HIV-seropositive and HIV-seronegative individuals were mostly attributed to AIDS-related conditions[8, 11]. However, since the introduction of ART, incidence rates for AIDS-related conditions have declined, but incidence rates for non-AIDS-related conditions among people with HIV has been increasing[11, 15]. One study estimated that among a cohort of nearly 40,000 patients initiating ART between 1996 and 2006, over 50% of causes of death were not AIDS-related[17]. Another study estimated that 70% of causes of death were not AIDS-related among a cohort of nearly 50,000 individuals in Europe, Australia, and the US receiving care between 1999 and 2011[18]. Among non-AIDS-related deaths, the leading causes of death were non-AIDS malignancies, cardiovascular disease, and liver disease[17, 18]. Reducing non-AIDS-related conditions continues to be an important priority for improving health outcomes and survival among people with HIV.

Evidence suggests that relative to the general population, people with HIV are at an increased risk for many non-AIDS conditions that are associated with aging, and these include cardiovascular disease, some cancers, renal disease, lung disease, liver disease,

osteoporosis, neurocognitive disorders, and frailty[19]. Many of these increased risks among people with HIV persist even after accounting for treatment and traditional risk factors[19]. From 1992 to 2003, a US prospective cohort study of 54,780 individuals found higher incidence rates for anal, colorectal, liver, lung, renal, and vaginal cancer; Hodgkin lymphoma, leukemia, and melanoma for those with HIV than in the general population after adjustment for age, sex, and race[20]. A systematic reviewed estimated that the risk ratio for cardiovascular disease comparing people with HIV not on ART to the general population was 1.61 [95% CI: 1.43, 1.81], while it was 2.00 [95% CI: 1.70, 2.37] comparing people with HIV on ART to the general population[21]. There is also concern that people with HIV may also be experiencing some aging-related conditions at earlier ages[15, 19]. A case-control study with over 10,000 Italian participants who were 46 years old on average between 2002 and 2009, found that the prevalence of noninfectious comorbidities for each age stratum was higher for those with HIV than in matched controls[19].

The exact mechanisms for these differences remain unclear, but researchers hypothesize that accelerated aging processes in people with HIV are likely to occur through processes that influence immunodeficiency and chronic inflammation[15, 22]. Specifically a combination of processes that include oxidative stress, telomere inhibition, telomere shortening, and lamin A mutations and accumulations are likely to result in increased risks for many of these aging processes and conditions among people with HIV[22]. A study among 486 South Africans examined two validated biomarkers of aging, and found shorter telomere length and higher CDKN2A, both reflective of older age, among HIV-seropositive individuals compared to HIV-seronegative individuals[23]. These processes could result

from the presence of HIV infection itself, the side effects of ART, or an increased burden of risk factors that promote aging among people with HIV[15, 22, 23].

One aging-associated condition, frailty, is a syndrome of physical weakness that has been associated with higher risks of falls, hospitalization, institutionalization, and death[24, 25]. The Fried Frailty Index (henceforth, FFI), a tool validated in the Cardiovascular Health Study (CHS), is one measure used to operationalize the frailty phenotype based on five components: weakness, slowness, unintentional weight loss, low activity, and exhaustion[24]. Frailty, disability, and comorbidity are often thought to be synonymous and highly concordant. Defined by the FFI, 46% of frail adults had at least one comorbid condition, 6% had activity daily living (ADL) disability, 22% had both comorbidity and ADL disability, and 27% did not have comorbidity or ADL disability[24]. Frail adults were at an increased risk for several outcomes, even after adjustment for age, gender, race, subclinical and clinical disease, disability, socioeconomic status, health status, depressive symptoms, income, and smoking status[24]. The adjusted hazard of death over a three-year period of follow-up among 5,317 individuals at least 65 years of age in the CHS was 1.63 for frail adults compared to non-frail adults [95% CI: 1.27, 2.08][24]. Frailty, a syndrome of physical weakness, is an aggregate expression of decreased physiological function that is associated with age or disease[24, 26].

Another prospective cohort study with over 40,000 participants in the Women's Health Initiative- Observational Study (WHI-OS) aged 65-79 found that over three years of follow-up, frail women had 1.71 times the hazard of death [95% CI: 1.48, 1.97] and 1.57 times the hazard of hip fracture [95% CI: 1.11, 2.20], adjusting for other factors including comorbid conditions[25]. Over the same period of follow-up, frail women had 1.95 times the

risk of number of average hospitalizations [95% CI: 1.72, 2.22] and 3.15 times the risk of incident ADL disability [95% CI: 2.47, 4.02] compared to non-frail women, adjusting for other factors[25]. Among 1230 participants from aging injection drug users (IDUs) in the AIDS Linked to the IntraVenous Experience (ALIVE) cohort, HIV-negative frail IDUs had 2.63 times the rate of death compared to HIV-negative non-frail IDUs [95% CI: 1.23, 5.66], while HIV-positive non-frail IDUs had 3.29 times the rate of death [95% CI: 1.85, 5.88], and HIV-positive frail IDUs had 7.06 times the rate of death [95 CI: 3.49, 14.30], after adjustment for age, gender, race, education, and comorbid conditions[27].

Frail adults also have higher healthcare expenditures relative to the non-frail[28, 29]. A recent study of a cohort of older people from two Australian states found that healthcare costs increased 22% and 43% over a six-month period for individuals with intermediate and high frail status, respectively, compared to non-frail individuals[29]. Another recent study of a cohort of older Germans aged 50-75 found an association between frailty and increased healthcare costs, adjusting for socio-demographic factors and comorbidity[28]. This study found that the average total healthcare costs for non-frail individuals over a three-month period were €642, followed by €1014 for pre-frail individuals, €1616 for frail individuals with three components, and €3659 for frail individuals with four or five components[28].

A systematic review of twenty-one community-based cohorts of individuals aged 65 and older shows that global frailty prevalence in the general population varies widely, ranging from 4% to 59%, with a weighted average of 10.7%[30]. One study among a nationally representative sample of 7,439 Medicare enrollees aged 65 years and older in the National Health and Aging Trends Study estimated US frailty prevalence at 15% in

2011[31]. Research on interventions among frail individuals have targeted the prevention of worsening frailty and the improvement of clinical outcomes following the onset of frailty[32, 33]. Using the FFI, limited studies in the general population of women aged 70-79 have found slowness, weakness, and low physical activity to be the most common frailty criteria[24, 33]. Some studies suggest that exercise and nutritional interventions can delay the onset of frailty and improve its symptoms[34-37]. One study among 216 frail participants in Sydney, Australia who were 83 years old on average treated by clinicians working within rehabilitation and aged care services, found that tailored interventions targeting identified characteristics of frailty reduced frailty and improved mobility over a 12-month period compared to usual care[33]. For example, these tailored interventions for meeting each individual frailty component could include consultation with a dietitian for weight loss, referral to a psychiatrist for exhaustion, home-based physiotherapy sessions for weakness, or several other interventions[33]. Studies show that resistance exercise training can increase strength in older adults, despite age-associated decreases in muscle mass[34].

In addition to older adults, women, racial/ethnic minorities, those with low socioeconomic status, and people with HIV are more likely to be frail[24, 31, 38]. After validating the FFI, the CHS estimated baseline frailty prevalence was higher among women than men (7% vs. 5%)[24]. Among participants in the National Health and Aging Trends Study frailty prevalence was also higher among women than men (17% vs. 13%)[31]. The same study estimated that the prevalence of frailty among Hispanics and black non-Hispanics was 25% and 23%, respectively, while it was 14% for white non-Hispanics[31]. Another cross-sectional analysis in the Women's Health and Aging Studies among 727 women aged 65 and older, observed that women with less than a high school education

were 3.0 times as likely to be frail than those with more than a high school education [95% CI: 2.0, 4.5], adjusting for age, race, insurance status, smoking status, and comorbidities[39]. Women with an annual household income less than $10,000 were 2.0 times as likely to be frail [95% CI: 1.3, 3.2], adjusting for other factors[39]. This study observed that blacks were more likely to be frail than whites in unadjusted models, race was no longer associated with frailty after including measures of socioeconomic status in adjusted models (OR = 0.98 [95% CI: 0.64, 1.98])[39].

A systematic review focusing on cohorts of people with HIV primarily in the US found that frailty prevalence ranged from 5% to 29%[40]. However, in this review, the highest median age was 57 years, compared to the previous review estimating a weighted frailty prevalence of 11% among adults aged 65 and older in the general population. In studies with HIV-seronegative controls, the prevalence of frailty was consistently higher at earlier ages for people with HIV[40]. A recent cross-sectional analysis of the Women's Interagency HIV Study (WIHS) among 2,028 women who were on average 39 years of age using frailty data from 2005 found 17% and 10% frailty prevalence among women with HIV and women at risk for HIV, respectively[38]. These data suggest that frailty is more common among people with HIV, and the prevalence of frailty among younger people with HIV may be comparable to those aged 65 and older in the general population.

There are limited studies describing the distribution and most common combinations of frailty components in the general population, but this remains unknown for PLWH in the US. The Australian study among receiving rehabilitation and aged care services, found that low physical activity and exhaustion were the most common frailty components at 65% and 63%, followed by weakness at 7% among older adults with a

mean age of 83 years[33]. Given that in this population, tailored interventions targeting individual frailty components reduced frailty and improve mobility over a 12-month period among frail adults, it is important to examine and identify whether similar frailty components can be targeted among people with HIV[33]. Identification of common frailty components among people with HIV can serve as targets in pinpointing those who could benefit from interventions that help prevent frailty among non-frail adults and lessen the severity of frailty among frail adults.

There are limited longitudinal studies of frailty in the US general population. The original study validating the FFI among 5,317 men and women at least 65 years old in the CHS reported the four-year risk of frailty was 7%[24]. The Women's Health Initiative Observational Study (WHI-OS) among a nationally representative sample of 40,657 women in the general population aged 65-79 reported the three-year risk of frailty was 15%[25]. To our knowledge there are only two longitudinal studies of frailty in people with HIV, and both were conducted in the MACS cohort which includes only men[41, 42]. In the MACS, assessing data on 2,150 men from each six-month visit collected between 1994 and 1996, men with HIV across all durations of infection had a higher prevalence of frailty than men without HIV[41]. Looking across all visits, this study estimated that men with HIV were 11.0 times (95% CI: 6.4, 18.9) as likely to be frail compared to men with HIV, and men with longer durations of HIV were associated with increased frailty prevalence[41]. The estimated frailty prevalence for a 55-year-old man who had been living with HIV infection no more than four years was 3.4% (95% CI: 1.3, 8.6), and the same as an HIV-uninfected man of the same race/ethnicity and education who was at least 65 years old[41]. Another MACS analysis on 1,946 men found that between 2007 and 2011, the odds of developing

frailty was associated with a history of AIDS but not with HIV infection alone[42]. After adjustment for other factors, men with HIV and a history of AIDS were 2.3 times as likely to become frail over the next study visit compared to men without HIV (95% CI: 1.5, 3.4)[42]. Though women are more likely to develop frailty, there are no longitudinal studies of frailty among women with HIV and the risk of frailty remains unknown in this population

Some studies have suggested there may be a link between smoking and frailty[25, 38, 42, 43]. Cross-sectional studies have reported higher frailty prevalence among smokers than in non-smokers among those 65 years and older[25, 38, 44]. Limited longitudinal data on smoking and frailty have suggested that smoking is an independent risk factor for frailty in the general population[25, 43]. Smoking is a cause of many chronic diseases associated with aging, including cardiovascular disease, respiratory disease, and cancer[45, 46]. For example, among a nationally representative sample of US adults aged 35 and older, it was estimated that in 2011, 48.5% of deaths from 12 cancer sites were attributable to cigarette smoking; these sites included cancers of the colorectum, esophagus, kidney and renal pelvis, larynx, liver and intrahepatic bile duct, myeloid leukemia, oral cavity and pharynx, pancreas, stomach, urinary bladder, uterine cervix, and lung, bronchus, and trachea[47]. The CDC estimates that 33% of deaths from cardiovascular disease are attributable to cigarette smoking[46]. There are several pathways by which smoking causes a variety of diseases, which can include increased levels of inflammatory markers and enhanced oxidative stress[48].

Smoking is more common among people with HIV than in the general population[49, 50]. A nationally representative study among over 30,000 US adults from the Medical Monitoring Project and National Health Interview Survey estimated that while smoking

prevalence was 21% among US adults in the general population in 2009, it was 42% among people with HIV receiving medical care[49]. People with HIV who smoke are at increased risk for many HIV-related and non-HIV-related conditions compared to people with HIV who do not smoke, a few of which include bacterial pneumonia, lung cancer, heart disease, and COPD[51-53]. As mentioned previously, HIV infection is also an important risk factor for many of these aging-associated conditions, independent of traditional risk factors such as smoking[54]. It is presumed that one pathway by which smoking and HIV infection can cause aging-related disease is through their independent associations with increased levels of inflammatory markers[54]. It is plausible that some of the same mechanisms by which smoking causes aging-related disease among people with HIV can similarly result in increased frailty among this population [53].

Smoking is a modifiable risk factor that could have a high impact for reducing frailty among people with HIV, where smoking is highly prevalent. To our knowledge, there are no US studies estimating the independent effect of smoking on incident frailty. In the WHI-OS cohort, current smokers were 2.9 times as likely to develop frailty over a three-year period of follow-up compared to never smokers (95% CI: 2.4, 3.6)[25]. However, though a risk factor for frailty, the independent effect of smoking on the risk of frailty adjusting for other confounding factors was not determined. One recent longitudinal study among a nationally representative sample of 2,542 adults aged 60 and older in England found an independent association between current smoking and the four-year risk of frailty (OR = 1.60; 95% CI: 1.02, 2.51)[43]. The effect of smoking on frailty among people with HIV remains unknown.

CHAPTER 2. SPECIFIC AIMS

This project will use data from a prospective, interval cohort of participants in the Women's Interagency HIV Study (WIHS). Comparing women with HIV and women without HIV, this research aims to:

Aim 1: Evaluate the distribution of frailty components among both frail and non-frail women. Using current data, we hypothesize that the most common frailty component and most common combination of frailty components will differ between women with HIV and women without HIV due to potential differences in the processes of biological aging.

Aim 2: Assess the one-year risk of frailty. Using existing data from 2015 to 2017, we hypothesize that the incidence of frailty will be higher in women with HIV compared to women at risk for HIV, due to accelerated aging processes among the expanding population of people with HIV.

Aim 3: Estimate the effect of smoking on the one-year risk of frailty. Using existing data from 2015 to 2017, we hypothesize that the effect of smoking on incident frailty will be higher for women with HIV compared to women at risk for HIV due to smoking-related increases in the risk of both HIV-related and non-HIV-related conditions, including premature death, among people with HIV.

CHAPTER 3. METHODS

DATA SOURCE

This project will use observational data from the WIHS cohort. The WIHS was established in August 1993, making it the largest U.S. cohort study of women with or at-risk for HIV infection[55]. Until 2012, the WIHS was comprised of six consortia, some of which comprised multiple clinical subsites[55]. These six WIHS sites were located in Bronx/Manhattan, NY; Brooklyn, NY; Los Angeles/Southern California/Hawaii; San Francisco, CA; Chicago, IL; and Washington, DC (shown in Figure 1). The WIHS initially enrolled 2,059 HIV-positive women and 569 HIV-negative women between October 1, 1994 and November 15, 1995, and another 738 HIV-positive women and 403 HIV-negative women between October 1, 2001 and September 30, 2002[55, 56]. Beginning in 2013, the WIHS closed its Los Angeles/Southern California/Hawaii consortium and added four new Southern sites, including Atlanta, GA; Chapel Hill, NC; Miami, FL; and Birmingham, AL/Jackson, MS (Figure 1)[57].

The WIHS is a prospective, interval cohort with semi-annual follow-up visits[64, 65]. The WIHS includes interview, physical examination, and laboratory data from HIV-positive women and HIV-negative women, aged 18 years and older, recruited from primary care clinics, hospital-based programs, research programs, community outreach sites, women's support groups, drug rehabilitation programs, HIV testing sites, and referrals from enrolled

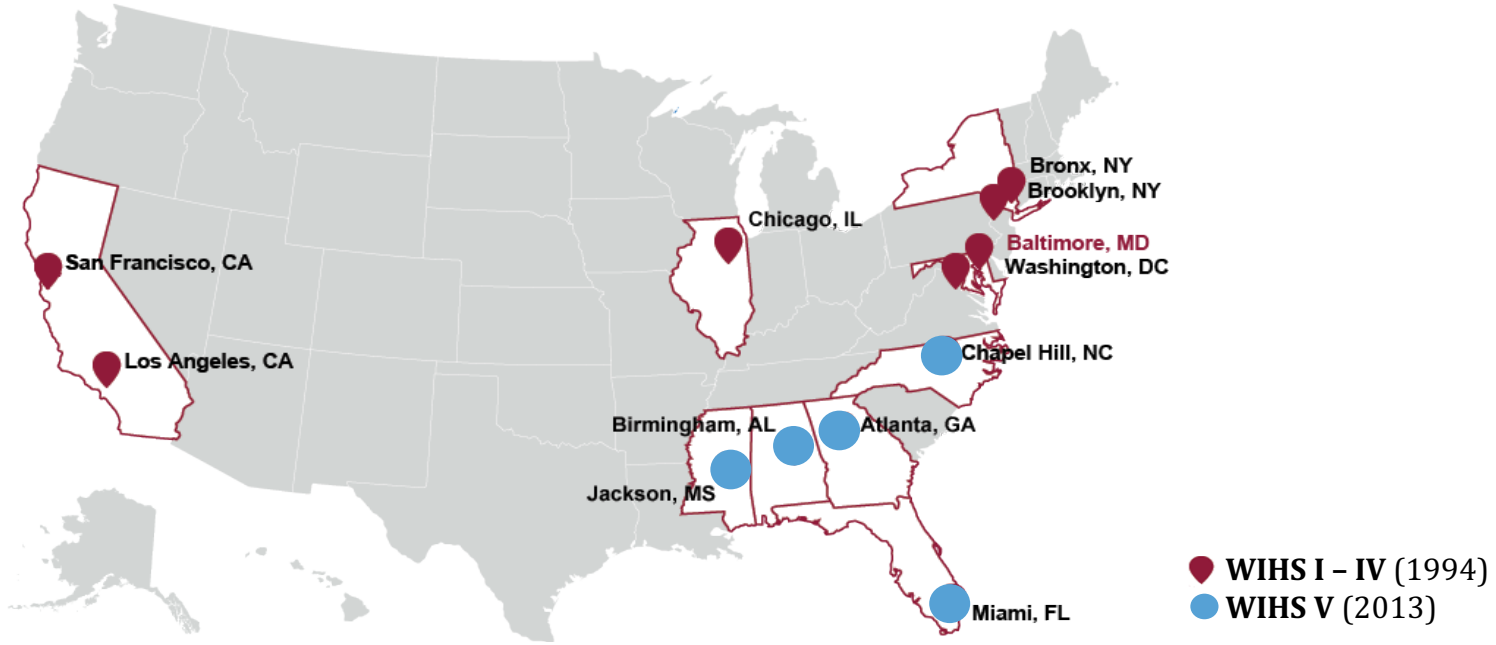
participants[55, 56]. At these semiannual visits, the following data are collected: medication data including a detailed form on medications used as prophylaxis and/or treatment and adherence; physical and gynecologic examinations; detailed questionnaires regarding medical history, health services utilization, sexual behaviors, demographics and psychosocial characteristics; neuropsychological screening and examination; and laboratory testing of specimens, including plasma and serum for CD4+ T-cells and HIV-1 RNA viral load[55, 56]. Institutional review board approval was obtained at each site and written informed consent was obtained from all women.

The WIHS was actively following 2,363 women as of 2016[57]. The median age was 51 (Interquartile Range [IQR]: 44, 56) for women with HIV and 49 (IQR: 41, 55) for women without HIV[57]. The majority of the WIHS cohort is non-white; 72% of women are black non-Hispanic, 15% are Hispanic, 10% are white non-Hispanic, and 4% are other racial groups. Across all waves, 25% of participants have died (9% for HIV-; 31% for HIV+) and 8% were lost to follow-up (12% for HIV-; 7% for HIV+)[57]. About one-third of the cohort has less than a high school education (31% for HIV-; 33% for HIV+) and the majority of participants report an annual household income no more than $18,000 (56% for HIV-; 64% for HIV+)[57]. Women with HIV are more likely to report having health insurance (95%) than women without HIV (79%). The proportion of women who reported injection drug use (IDU) at study entry is 15%, but only 1% of women reported current IDU in the past six months[57].

With respect to clinical characteristics of the WIHS cohort, the median CD4 cell count is 628 (IQR: 435, 853) for women with HIV compared to 1011 (IQR: 815, 1280) for women without HIV[57]. The majority of women with HIV have an undetectable viral load

that is less than 20 copies/mL (69%)[57]. Among all women in the cohort, 21% have diabetes, 15% have history of an adverse cardiovascular event, and 5% have history of cancer[57]. Lastly, 9% of women have active hepatitis C virus (HCV) infection confirmed by positive HCV RNA testing (7% for HIV-; 10% for HIV+)[57].

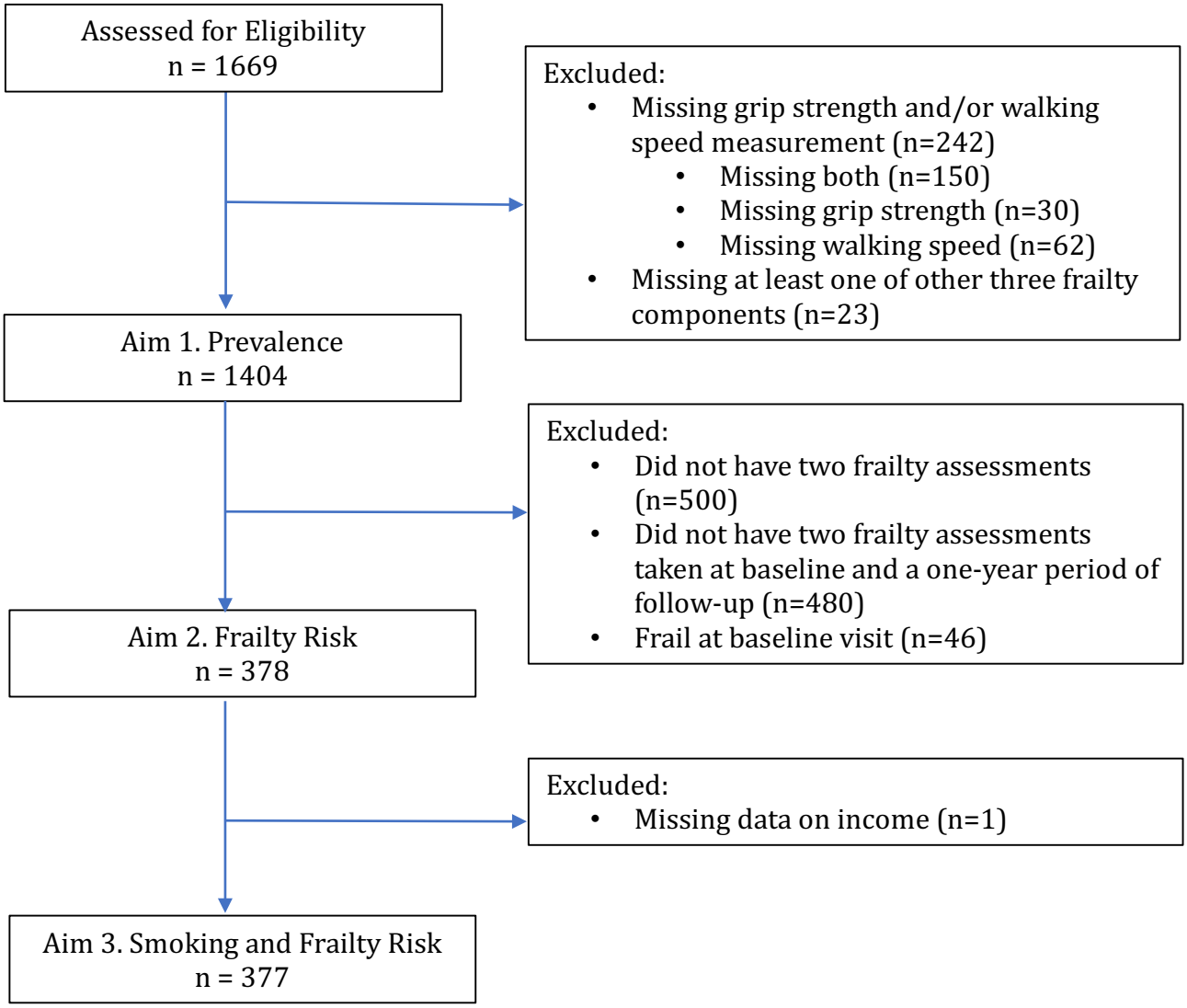
Figure 1. WIHS Sites, 2018.



INCLUSION AND EXCLUSION CRITERIA

The analyses for this project was restricted to women at least 40 years of age with at least one frailty assessment in the study period between October 1, 2015 and September 30, 2017, corresponding to WIHS visits 43 through 46. Of 1,669 women, there were 265 women with missing data on at least one component of the frailty outcome (Figure 2). Consequently, there were 1404 women in the study sample for aim 1; 378 women in the study sample for aim 2; and 377 women in the study sample for aim 3.

Figure 2. Flow Diagram of Study Eligibility, 2015-2017.



OUTCOME

For all three aims of this project, the outcome of interest was frailty. As a prospective, interval cohort, the WIHS has set dates for each six-month visit interval. Starting at WIHS visit 43, coincident with October 1, 2015, the WIHS protocol has included measurement of frailty components and assigned frailty status among women who are 40 years of age and older. The Fried Frailty Index (henceforth, FFI), a tool validated in the Cardiovascular Health Study (CHS), is used to operationalize the frailty phenotype based on five components: weakness, slowness, unintentional weight loss, low activity, and exhaustion[24]. Frail status was defined as exceeding the component-specific threshold (Table 1) for at least three frailty components, pre-frail status was defined as exceeding the threshold for two frailty components, and robust status was defined as exceeding the threshold for no more than one frailty component[24]. As in the CHS, two performance-based measures, grip strength and walking speed, operationalized the FFI components of weakness and slowness. Grip strength was measured by squeezing a Jamar dynamometer with maximum force using the dominant hand, and the highest value (greatest strength) of three attempts was used for analysis. Walking speed was measured in seconds by a timed four-meter walk, and the fastest time of two attempts was used for analysis. Three ongoing, prospectively collected self-reported measures in the WIHS operationalized the FFI components of unintentional weight loss, low activity, and exhaustion[38].

Performance-based measures are assessed at least every other semiannual visit. Exhaustion and low physical activity are assessed at every other semiannual visit and unintentional weight loss is assessed at each semiannual visit. For this project, the most recent performance-based measurement estimated frailty prevalence, and the most recent

two performance-based measurements estimated the one-year risk of frailty. If any of the self-reported frailty components were missing, the closest previous or subsequent value that occurred within two visits of each performance-based measurement was used. For this project, women who had missing data on grip strength and/or walking speed, and women who did not have self-reported measures within two visits of the performance-based measurement were considered incomplete cases and excluded (Figure 2).

Table 1. The Fried Frailty Index and operationalization of each frailty component in the Women's Interagency HIV Study.

Frailty Component	WIHS Operationalization
Unintentional weight loss	Since your last visit, have you had unintentional weight loss of at least 10 pounds? a. Yes[a,b] b. No
Exhaustion	During the past 4 weeks, as a result of your physical health, have you had difficulty performing your work or other activities? a. All of the time[a,b] b. Some of the time[a] c. None of the time
Low physical activity	Does your health now limit you in vigorous activities, such as running, lifting heavy objects, or participating in strenuous sports? a. Limited a lot[a,b] b. Limited a little[a] c. Not limited at all
Slowness (same as CHS)	4-meter walk at usual pace: a. ≥ 6.13 seconds for height ≤ 1.59 meters[a,b] b. ≥ 5.25 seconds for height > 1.59 meters[a,b] c. All other values
Weakness (same as CHS)	Grip strength measured by Jamar dynamometer: a. ≤ 17.0 kilograms for BMI ≤ 23[a,b] b. ≤ 17.3 kilograms for 23 < BMI ≤ 26[a,b] c. ≤ 18.0 kilograms for 26 < BMI ≤ 29[a,b] d. ≤ 21.0 kilograms for BMI >29[a,b] e. All other values

Abbreviations: WIHS, Women's Interagency HIV Study; CHS, Cardiovascular Health Study; BMI, Body Mass Index

[a]Indicates frailty component threshold met (main definition)

[b]Indicates frailty component threshold met (restricted definition)

EXPOSURE

For aim three, the two primary exposures of interest were current cigarette smoking status (smoker or non-smoker) and the number of cigarette smoking pack-years at the baseline visit. At each semiannual visit, women self-report smoking status, with women classified as current smokers if they answer "yes" to the following question: "Since your study visit on…have you smoked cigarettes?" Additional smoking data are collected at each semiannual visit and smoking pack-years were determined based on participants' self-reported average number of cigarettes or packs smoked per day. To calculate the number of smoking pack-years, the number of packs smoked per day was averaged across all visits with non-missing values and was multiplied by the number of years having smoked. As a sensitivity analysis, we compared our results with those using an alternate definition for smoking pack-years. If the self-reported average number of cigarettes or packs smoked per day at any semiannual visit was missing, the previous non-missing value was carried forward until it was replaced by the next non-missing value. To calculate the number of smoking pack-years using the alternate definition, the number of packs smoked per day across each visit was averaged and multiplied by the number of years having smoked.

COVARIATES

Covariates were determined at the performance-based measurement in prevalence analyses and at the baseline visit of the two performance-based measurements in analyses of frailty risk. If any values for covariates were missing, the last reported value was used. The following characteristics were used to describe participants:

- HIV status: based on results from enzyme-linked immunosorbent assay and western blot
    - indictor for HIV+ diagnosis
- Age: based on year of birth
- Race/ethnicity: based on participants' self-report
    - categorized as white non-Hispanic, black non-Hispanic, other non-Hispanic, Hispanic
- Education: based on participants' self-report
    - categorized as less than high school, high school, more than high school
- Annual household income: based on participants' self-report
    - categorized as ≤$6,000, $6,001-12,000, $12,001-18,000, $18,001-24,000, >$24,000
- Region: based on geographic location of participants' WIHS site
    - categorized as Midwest, Northeast, South, West
- Current cigarette smoking status: based on participants' self-report
    - categorized as smoker, non-smoker, former smoker
- Weekly alcohol use: based on participants' self-report
    - categorized as 0 drinks, 0.1-7 drinks, 7.1-12 drinks, > 12 drinks
- Other substance use: based on participants' self-report
    - indicator for use of the following recreational drugs:
        - crack cocaine, cocaine, heroin, methadone, methamphetamines, amphetamines, marijuana, prescription drug abuse, or other recreational drug use

- Active hepatitis C infection: based on results from HCV RNA testing
    - indicator for HCV+ result
- HIV viral load: based on results from HIV RNA quantification assays
- CD4 cell count: based on results from flow cytometry

For aim three, a conceptual model (Figure 3) informed by the literature provided a foundation for hypothesized relationships between the exposure of smoking, the outcome of frailty, and various factors. The conceptual model was used to build a directed acyclic graph (DAG) (Figure 4), and the following covariates were included in analyses as potential confounders: age (continuous), race/ethnicity (black non-Hispanic, all other races), education (<high school, high school, and >high school), annual household income (≤12,000, >$12,000), region (Midwest, Northeast, South, and West), heavy weekly alcohol use (≤7 drinks, >7 drinks), and any other recreational drug use (yes, no).

Figure 3. Conceptual Model.

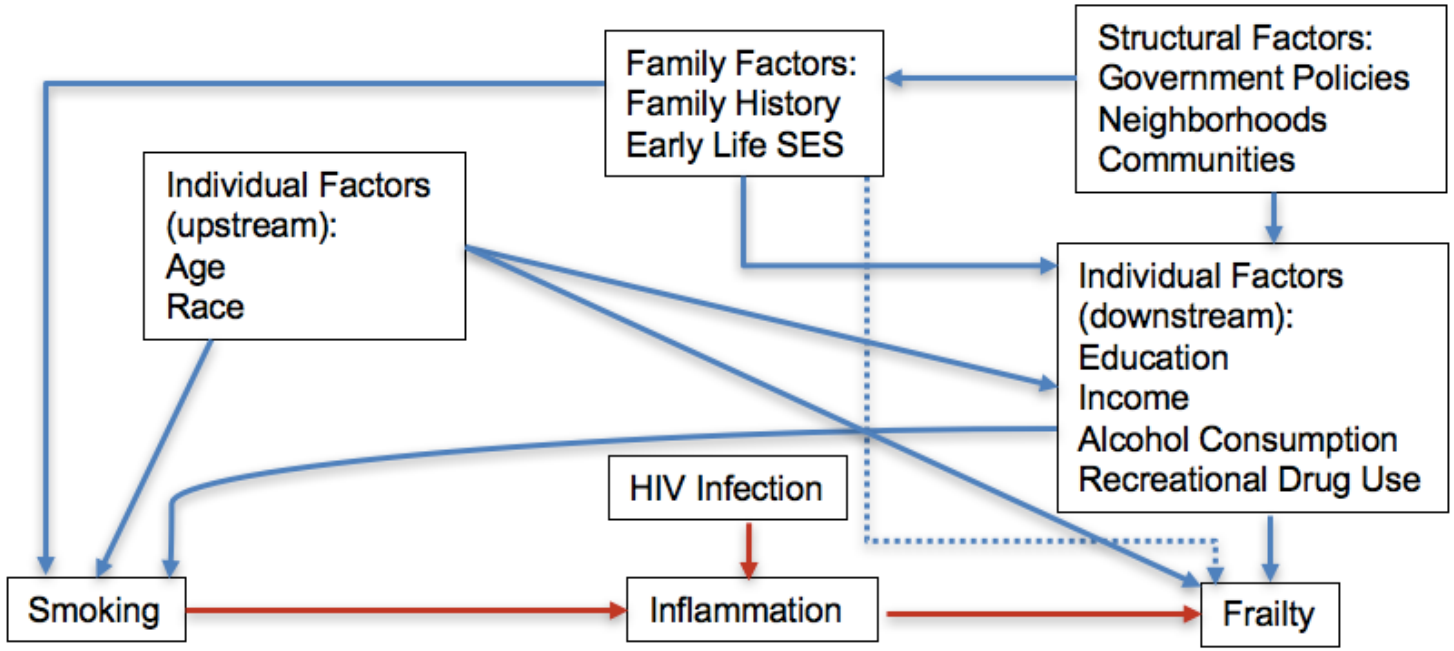
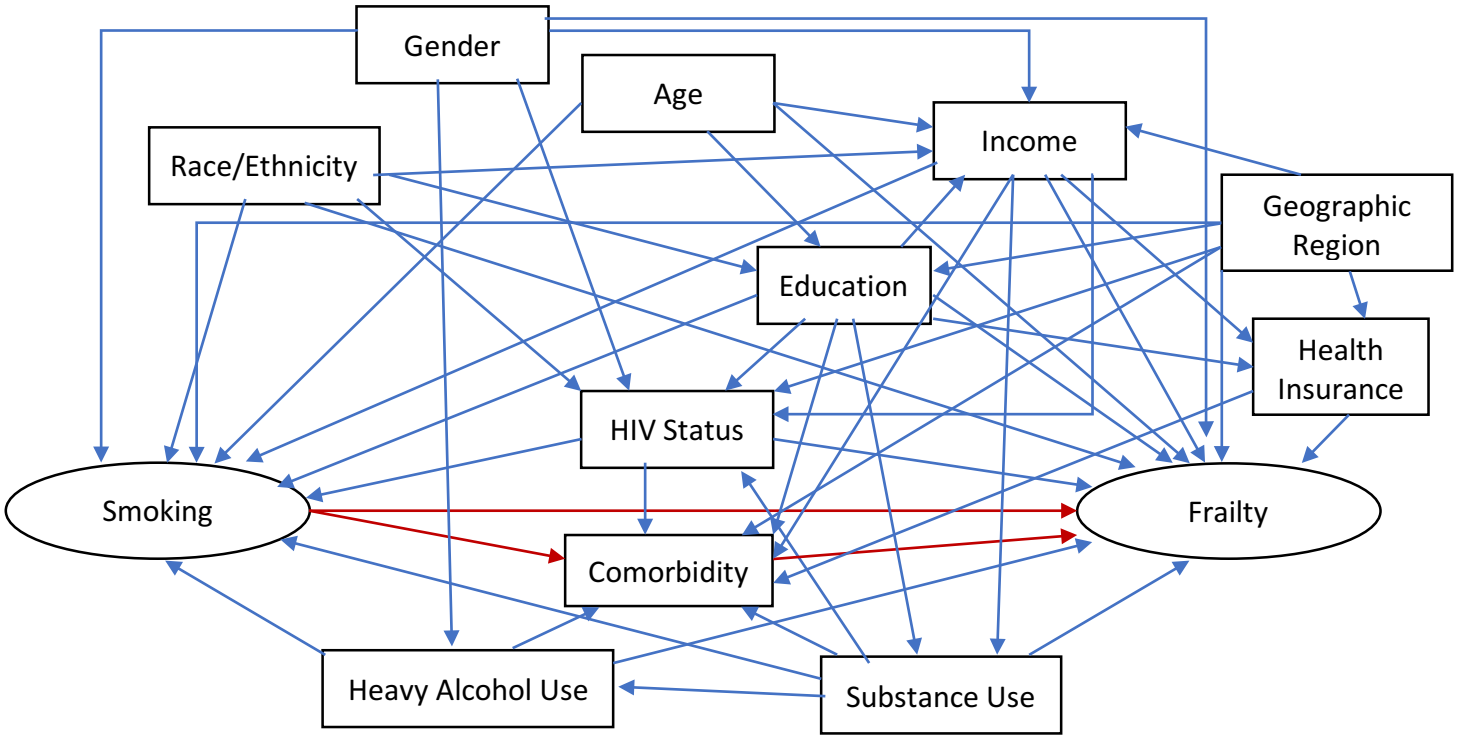


Figure 4. Directed Acyclic Graph (DAG) for Smoking and Frailty.



STATISTICAL ANALYSES

AIM 1

For aim one, participant characteristics were summarized using counts and percentages, by HIV status. Frailty prevalence was calculated as the proportion of women who exceeded the threshold for at least three of five frailty components within the study period. We conducted two sensitivity analyses, first to assess the robustness of results to our chosen definition of frailty by using a restricted definition of frailty (shown in Table 1) that includes only the highest values for exhaustion and low physical activity. For example, women had to respond "all the time" to the question, "During the past 4 weeks, as a result of your physical health, have you had difficulty performing your work or other activities?" in meeting the component-specific threshold for exhaustion. Also, in contrast to the previous WIHS analysis,[38] we chose to use the cut points for grip strength and walking speed that were validated in the general population by Fried (shown in Table 1), rather than using the highest and lowest quintiles of the distributions from our HIV-seronegative population for walking speed and grip strength, respectively. As a second sensitivity analysis, we compared our results to results obtained when using the average cut points in the previous WIHS analysis for the highest and lowest quintiles for the grip strength and walking speed measures, respectively. Data analyses were performed using SAS software version 9.3 (SAS Institute, Inc., Cary, NC).

AIM 2

For aim two, participant characteristics were summarized using counts and percentages, by HIV status. The one-year risk of frailty was estimated as the proportion of women from the population at-risk who developed frailty over the one-year risk period. Log-binomial models were used to estimate crude and age-adjusted one-year frailty risk ratios with 95% confidence intervals (CIs), comparing women with HIV to women without HIV. Linear binomial models were used to estimate crude and age-adjusted one-year frailty risk differences with 95% CIs, comparing women with HIV to women without HIV. Data analyses were performed using SAS software version 9.3 (SAS Institute, Inc., Cary, NC).

AIM 3

For aim three, participant characteristics were summarized according to current smoking status using percent or median with interquartile range (IQR), as appropriate. Potential confounders were hypothesized from the literature and identified using a directed acyclic graph (Figure 4)[58]. Stabilized inverse-probability-of-treatment weights were used to produce estimates for the one-year risk of frailty comparing current smokers to non-smokers, and were constructed using two logistic regression models. The first model estimated the unconditional probability of being a current cigarette smoker, and the second model estimated the probability of being a current cigarette smoker conditional on measured covariates. The final stabilized weight for the exposed was the marginal probability of being a current cigarette smoker divided by the participant's conditional probability of being a current cigarette smoker. The final stabilized weight for the unexposed was the marginal probability of not being a current cigarette smoker divided by

the participant's conditional probability of not being a current cigarette smoker. Key confounders were chosen to be included in the most parsimonious final weighted (adjusted) models if they were associated with the exposure in the conditional logistic regression model ($p<0.05$). A weighted log-binomial model was used to estimate multivariable-adjusted risk ratios (RR) for the one-year risk of frailty comparing current smokers to non-smokers. A weighted linear-binomial model was used to estimate multivariable-adjusted risk differences (RD) for the one-year risk of frailty comparing current smokers to non-smokers. Confidence intervals (CIs) were based on the robust (Huber-White) variance estimator. Smoking pack-years was categorized into quintiles to relax linearity assumptions. The two highest quintiles of the exposure distribution demonstrated a similar magnitude of effect on the one-year risk of frailty and were chosen as the cutoff for the final contrast comparing high to low cumulative smoking exposure in pack-years (≤7.5, >7.5). As described above, stabilized inverse probability of treatment weights were similarly used to estimate the one-year risk of frailty comparing women whose cumulative smoking exposure was greater than 7.5 pack-years to women whose cumulative smoking exposure was no more than 7.5 pack-years and were constructed using two logistic regression models. The first model estimated the unconditional probability of smoking >7.5 pack-years and the second model estimated the probability of smoking >7.5 pack-years conditional on measured covariates. The final stabilized weight for the exposed was the marginal probability of smoking >7.5 pack-years divided by the participant's conditional probability of smoking >7.5 pack-years. The final stabilized weight for the unexposed was the marginal probability of smoking ≤7.5 pack-years divided by the participant's conditional probability of smoking ≤7.5 pack-years. After adjustment for key

confounders, weighted log-binomial and linear binomial models were used to estimate multivariable-adjusted RRs and RDs for the one-year risk of frailty comparing women whose cumulative smoking exposure was greater than 7.5 pack-years to women whose cumulative smoking exposure was no more than ≤7.5 pack-years.

As a sensitivity analysis, we compared our results with those using an alternate definition for smoking pack-years. If the self-reported average number of cigarettes or packs smoked per day at any semiannual visit was missing, the previous non-missing value was carried forward until it was replaced by the next non-missing value. To calculate the number of smoking pack-years using the alternate definition, the number of packs smoked per day across each visit was averaged and multiplied by the number of years having smoked. Data analyses were performed using SAS software version 9.3 (SAS Institute Inc., Cary, NC).

CHAPTER 4. PREVALENCE AND ONE-YEAR RISK OF FRAILTY

Introduction

Many high-income countries, including the United States (US), have seen a shift in population demographics to older ages[1, 2]. Between 1970 and 2014, US life expectancy at birth increased from 70.8 years to 78.9 years[3]. People with HIV are also living longer due to the increased effectiveness and use of antiretroviral therapy (ART)[8, 11]. One recent study estimated that 20-year-olds on ART can expect to live into their early 70s[8]. By 2020, it is estimated that more than half of people with HIV in the US will be age 50 or older[14, 59]. Despite increased life expectancy, some evidence suggests that people with HIV may be experiencing aging-related conditions at earlier ages relative to the general population[15, 38].

One of these aging-related conditions, frailty, is a syndrome of physical weakness that has been associated with higher risks of falls, hospitalization, institutionalization, and death[24, 25]. Frail adults also have higher healthcare expenditures relative to the non-frail[28, 29]. One study among a nationally representative sample of 7,439 Medicare enrollees aged 65 years and older in 2011 estimated frailty prevalence at 15%[31]. In addition to older adults, people with HIV, women, racial/ethnic minorities, and those with low socioeconomic status (SES) are more likely to be frail[24, 31, 38]. A recent analysis of the Women's Interagency HIV Study (WIHS) among 2,028 women who were on average 39

years of age using frailty data from 2005 found 17% and 10% frailty prevalence among women with HIV and women at risk for HIV, respectively[38].

There are few longitudinal studies of frailty, and to our knowledge only two were conducted among people with HIV; both were conducted in the Multicenter AIDS Cohort Study (MACS), which includes only men[41, 42]. Given that women are more likely to develop frailty, it is important to determine whether frailty incidence is similar between women with and without HIV. Though we know the characteristics of adults who are more likely to develop frailty, data are limited on the components of the frailty outcome itself, and the distribution of frailty components remains unknown among people with HIV in the US[24, 33]. Identification of common frailty components can serve as targets in pinpointing women who could benefit from interventions that help prevent frailty among non-frail adults and lessen the severity of frailty among frail adults.

This study estimated the prevalence and one-year risk of frailty among two vulnerable populations, women with HIV and women at risk for HIV. We also compared the distribution of individual frailty components, and investigated whether there were differences between women with HIV and women at risk for HIV. We hypothesized that frailty prevalence and incidence would be higher among younger women with HIV and estimates would be comparable to older women in the general population due to previous studies reporting a higher occurrence of frailty among people with HIV.

Methods

Study Sample

The WIHS is a prospective cohort of women with and at risk for HIV recruited from primary care clinics, hospital-based programs, research programs, community outreach sites, women's support groups, drug rehabilitation programs, HIV testing sites, and referrals from enrolled participants[55]. This study included data from eight WIHS sites located in Brooklyn, NY; San Francisco/Bay Area, CA; Chicago, IL; Washington, DC; Atlanta, GA; Chapel Hill, NC; Miami, FL; and Birmingham, AL/Jackson, MS[55-57]. Institutional review board approval was obtained at each site and written informed consent was obtained from all women. At semiannual follow-up visits, the WIHS collects a wide range of data, including demographic and psychosocial characteristics, medical history, and laboratory data including CD4 count and HIV viral load[55]. Methods have been described in detail elsewhere[55-57]. The sample analyzed here included 1,404 women who were at least 40 years of age and had at least one frailty assessment between October 1, 2015 and September 30, 2017. Women with two frailty assessments over approximately a one-year period of follow-up were included in analyses estimating the one-year risk of frailty. Of these 1,404 women, 424 had frailty assessments taken at both baseline and a one-year period of follow-up. Due to frail status at baseline, 46 women were excluded, resulting in a sample of 378 women to estimate the one-year risk of frailty.

Outcome definition

Starting on October 1, 2015, the WIHS protocol has included measurement of frailty components and assigned frailty status among women who are 40 years of age and older.

The Fried Frailty Index (FFI), a tool validated in the Cardiovascular Health Study (CHS), was used to operationalize the frailty phenotype based on five components: weakness, slowness, unintentional weight loss, low activity, and exhaustion[24]. Frail status was defined as exceeding the component-specific threshold (Table 1) for at least three frailty components, pre-frail status was defined as exceeding the threshold for two frailty components, and robust status was defined as exceeding the threshold for no more than one frailty component[24]. As in the CHS, two performance-based measures, grip strength and walking speed, operationalized the FFI components of weakness and slowness. Grip strength was measured by squeezing a Jamar dynamometer with maximum force using the dominant hand, and the highest value (greatest strength) of three attempts was used for analysis. Walking speed was measured in seconds by a timed four-meter walk, and the fastest time of two attempts was used for analysis. Three ongoing, prospectively collected self-reported measures in the WIHS operationalized the FFI components of unintentional weight loss, low activity, and exhaustion[38].

Performance-based measures are assessed at least every other semiannual visit. Exhaustion and low physical activity are assessed at every other semiannual visit and unintentional weight loss is assessed at each semiannual visit. The most recent performance-based measurement estimated frailty prevalence, and the most recent two performance-based measurements estimated the one-year risk of frailty. If any of the self-reported frailty components were missing, the closest previous or subsequent value that occurred within two visits of each performance-based measurement was used. Women who had missing data on grip strength (n=30), walking speed (n=62), or both (n=150), and women who did not have self-reported measures within two visits of the performance-

based measurement (n=23), were considered incomplete cases and thus excluded. This resulted in the final prevalence sample of 1,404 women. For women with missing data on performance-based measurements, we found that the distributions for HIV status and the other three components among excluded women were similar to those of women included in our analyses.

Participant Characteristics

Participant characteristics were determined at the performance-based measurement in prevalence analyses and at the baseline visit of the two performance-based measurements in incidence analyses. If any values for participant characteristics were missing, the last reported value was used. The following characteristics were used to describe participants: HIV status (HIV+, HIV-), age (40-84 years), race/ethnicity (white non-Hispanic, black non-Hispanic, other non-Hispanic, Hispanic), education (less than high school, high school, more than high school), annual household income (less than or equal to $6,000, $6,001-12,000, $12,001-18,000, $18,001-24,000, more than $24,000), region (Midwest, Northeast, South, West), cigarette smoking status (never, former, current), weekly alcohol use (0 drinks, 0.1-7 drinks, 7.1-12 drinks, more than 12 drinks), other substance use (yes, no), and active hepatitis C infection (RNA+, RNA-) . HIV-specific characteristics were HIV viral load (20-722,000 copies/mL) and CD4 cell count (6-2,283 cells/mm^3).

Statistical Analysis

Participant characteristics were summarized using counts and percentages, by HIV status, for the prevalence and incidence samples. Frailty prevalence was calculated as the proportion of women who exceeded the threshold for at least three of five frailty components within the study period. The one-year risk of frailty was estimated as the proportion of women from the population at-risk who developed frailty over the one-year risk period. Log-binomial models were used to estimate crude and age-adjusted one-year frailty risk ratios with 95% confidence intervals (CIs), comparing women with HIV to women without HIV. Linear binomial models were used to estimate crude and age-adjusted one-year frailty risk differences with 95% CIs, comparing women with HIV to women without HIV.

We conducted two sensitivity analyses, first to assess the robustness of results to our chosen definition of frailty by using a restricted definition of frailty (shown in Table 1) that includes only the highest values for exhaustion and low physical activity. In contrast to the previous WIHS analysis,[38] we chose to use the cut points for grip strength and walking speed that were validated in the general population by Fried, rather than using the highest and lowest quintiles of the distributions from our HIV-seronegative population for walking speed and grip strength, respectively. As a second sensitivity analysis, we compared our results to results obtained when using the average cut points in the previous WIHS analysis for the highest and lowest quintiles for the grip strength and walking speed measures, respectively. Data analyses were performed using SAS software version 9.3 (SAS Institute, Inc., Cary, NC).

Results

Baseline characteristics of the prevalence and incidence samples are presented in Table 2. The median age was 52 years (interquartile range [IQR]: 47, 57) for both women with HIV and women without HIV. The majority of women were black non-Hispanic (75%), followed by white non-Hispanic (11%). Figure 5 presents the proportion of women in each frailty category by HIV status and age group. The overall prevalence of frailty was 11.5% (n=161/1,404); 10.0% (n=103/1,025) among women with HIV and 15.3% among women without HIV (n=58/379). Frailty prevalence was consistently higher for women without HIV compared to women with HIV for all age groups, except the 55-59 age group. Similarly, using the restricted definition of frailty, frailty prevalence was higher among women without HIV than among women with HIV (4.2% overall prevalence of frailty (n=59); 3.3% among women with HIV (n=34) and 6.6% among women without HIV (n=25)). As expected, frailty prevalence increased with age (Figure 5). Using the average cut points for grip strength and walking speed from the previous WIHS analysis, the overall frailty prevalence was 21.9% (n=307) and similar for women with HIV (22.0%) and women without HIV (21.4%).

Figure 6 presents the prevalence of each frailty component by frailty status and HIV status. Low physical activity was the most frequently occurring frailty component regardless of frailty status (Figure 6). Exhaustion was the second most frequently occurring frailty component among frail and pre-frail women. The prevalence of frailty components was similar for women with and without HIV, except that it was consistently more common for women with HIV to report unintentional weight loss and for women without HIV to meet the definition for weakness, regardless of frailty status.

The most common combinations of frailty components among frail, pre-frail, and robust women were similar in women with and without HIV. The most common combinations of frailty components were low physical activity and exhaustion alone for pre-frail women, and in combination with one other component for frail women, which accounted for 67% and 68% of all frailty combinations in those groups, respectively (Figure 7). The severities of low physical activity and exhaustion were similar in women with and without HIV among frail, pre-frail, and robust women. Most robust women did not report low physical activity (60%) or exhaustion (97%) (Figure 8). In contrast, 68% and 20% of frail women reported the maximum value for low physical activity and exhaustion, respectively. Among frail women with HIV, the median grip strength and walking speed were 22.0 kg (IQR: 18.0, 28.0) and 5.5 seconds (IQR: 4.0, 7.9), respectively. Among frail women without HIV, the median grip strength and walking speed were 20.3 kg (IQR: 18.0, 30.0) and 5.6 seconds (IQR: 4.0, 7.5), respectively.

Table 3 presents the one-year risk of frailty, along with crude and age-adjusted risk ratios and risk differences comparing women with HIV to women without HIV. Overall, the one-year risk of frailty was 6.6% (95% CI: 4.1, 9.1) and was similar for women with HIV compared to women without HIV. For example, after adjusting for age, women with HIV were 0.91 times as likely to develop frailty over a one-year period compared to women without HIV (95% CI: 0.39, 2.10).

Discussion

In a predominantly low-income sample of US women with and at risk for HIV infection in the WIHS who were at least 40 years of age, the overall prevalence of frailty

was 11.5%. Frailty prevalence was higher for women without HIV than for women with HIV. The distributions of frailty components among the frail, pre-frail, and robust were comparable for women with and without HIV. Among all women, the most common component was low physical activity, and the most common combinations of components for both pre-frail and frail women included low physical activity and exhaustion. The one-year risk of frailty was 6.6%, and risks were similar for women with and without HIV.

The original study validating the FFI among 5,317 men and women at least 65 years old in the CHS reported 7% frailty prevalence and 7% four-year frailty risk[24]. The Women's Health Initiative Observational Study reported 16% baseline frailty prevalence among 40,657 women in the general population aged 65-79 who were recruited between 1993 and 1998, and 15% three-year frailty risk[25]. In our study population with a median age of 52 years, frailty prevalence and incidence estimates for women with and at risk for HIV were comparable to those from studies of individuals in the general population who were at least 65 years old. Previous cross-sectional studies, and limited longitudinal studies, have suggested that people with HIV are more likely to develop frailty[38, 41, 42]. In the MACS, using data collected between 1994 and 1996, men with HIV were more likely to be frail than men without HIV[41]. Another MACS analysis found that between 2007 and 2011, the odds of developing frailty was associated with a history of AIDS but not with HIV infection alone[42]. The previous WIHS analysis using frailty data from 2005 reported 15% overall frailty prevalence, and a higher frailty prevalence among women with HIV than in women at risk for HIV (17% vs. 10%)[38]. In our study population ten years later, frailty prevalence was higher in women at risk for HIV than in women with HIV, and the one-year risk of frailty was similar in both groups.

These differences could be due to several factors. First, the WIHS implemented an additional recruitment period from 2011-2012. The WIHS also added four new sites from the Southern US in 2013, and participants from these sites are younger compared to women in the existing cohort[57]. Unlike the previously published WIHS analyses, our data included women recruited from these two additional waves, and women from southern sites comprised more than one-third (38%) of our prevalence sample population. Second, the previous WIHS analyses included participants from earlier in the HIV epidemic. Since 2012, clinical guidelines have recommended that ART be provided to all HIV-seropositive patients, regardless of CD4 count[60]. Thus, participants from earlier analyses were less likely to be on ART and more likely to have experienced advanced HIV disease, which increases the risk of aging-associated conditions and mortality[8, 17, 19]. Lastly, we chose to use the cut points for grip strength and walking speed measures that were validated in the general population by Fried, in contrast to the previous studies in the WIHS and the MACS, which used the highest and lowest quintiles of the distributions from their HIV-seronegative populations for walking speed and grip strength, respectively, as the cut point for each measure. Here our approach allowed us to compare the performance on frailty measures of the WIHS population to the CHS population of women who were at least 65 years of age, thus reflecting the burden of frailty among women with and at risk for HIV relative to older populations. Our sensitivity analysis showed that when using the average cut points for each measure from the previous WIHS analysis, frailty prevalence increased to 21.9%, and was similar in women with and at risk for HIV.

A high prevalence and incidence of frailty among women at risk for HIV was not anticipated in these analyses. However, previous studies in the general population have

suggested that several characteristics are associated with frailty, which, in addition to older age and female gender, include minority race/ethnicity, lower SES, geographic location, comorbidities, poor nutrition, smoking, and possibly alcohol consumption[24, 31, 38, 39, 43] Recently, DNA methylation signatures of intravenous illicit drug use and hepatitis C infection have also been linked to frailty among men with HIV[61]. Several of these risk factors are highly prevalent in the WIHS population, and while hepatitis C infection was more prevalent among women with HIV, some other factors were more prevalent among women at risk for HIV in our study population. To ensure comparability to HIV-seropositive women, HIV-seronegative women with HIV-related risk characteristics, such as injection drug use, were targeted for recruitment into the WIHS[55]. HIV-seronegative women in the WIHS are also less likely than HIV-seropositive women to report having health insurance[57]. As a result, in our study population some characteristics associated with frailty are more common in women at risk for HIV than in women with HIV. For example, more HIV-seronegative women than HIV-seropositive women report current smoking (47% vs. 38%) and drinking more than twelve drinks per week (12% vs. 4%). It is possible that the high prevalence of these risk factors that promote aging and disparities in care contributed to the high frailty prevalence and incidence in HIV-seronegative women.

We know of no other US studies describing the frequencies and combinations of frailty components among people with HIV. One randomized trial of 241 frail individuals in Sydney, Australia, who were an average age of 83 years and receiving rehabilitation and aged care services, found that low physical activity and exhaustion were the most common frailty components at 65% and 63%, followed by weakness at 7%[33]. A cross-sectional study of 175 participants from an HIV outpatient unit in France found that low physical

activity and exhaustion were the most common frailty components at 40% and 39%, respectively[62]. However, they did not report the most frequent combinations of frailty components. In our population, similar to the Australian and French populations, we found that low physical activity and exhaustion were highly prevalent among frail and pre-frail women with and at risk for HIV. We also found that these two frailty components most commonly occurred in conjunction with each other among frail and pre-frail women. Given that recent studies suggest that exercise and nutritional interventions can delay frailty onset and lessen frailty severity, our study has identified common components that can serve as targets in identifying women who could benefit from these interventions[34-37, 63].

Our analyses are not without limitations. First, some women had missing data for performance-based measures (grip strength and walking speed) and were thus excluded. We examined the assumption that these missing data were not related to frailty status or HIV status and also assessed the reasons women reported for not wanting to participate in any performance-based measurements. Among eligible women who declined to complete any performance-based measurements within the study period (n=126), 10% explicitly reported reasons related to inability, illness, or tiredness, and the distribution of HIV status was similar to those included in our study. Second, frailty status is episodic, especially in the short-term[64]. The previous longitudinal analysis in the MACS, which used quintiles to define the component-specific thresholds for grip strength and walking speed, found that 4% of consecutive study visits reverted from frail to non-frail status[42]. However, without intervention, transitions to a higher degree of frailty are more common and complete reversal from frailty to robustness is rare among elderly people[64]. Given the limited longitudinal data in frailty research, especially among people with HIV, it is still of interest

to understand the short-term risk of frailty among women with and at risk for HIV. Future studies are needed to assess long-term trends and differences in frailty prevalence and incidence between women with and at risk for HIV, and to better understand the impacts of frailty variability on health outcomes. Third, estimates for the risk ratios and risk differences were imprecise. However, estimates for frailty prevalence and incidence were comparable between our population and the general population of women at least 65 years of age, and this pattern should be further examined[24, 25].

In conclusion, this study pinpointed common components of frailty among women with HIV and women at risk for HIV. Low physical activity and exhaustion were the most common frailty components among frail and pre-frail women, and low physical activity was the most common frailty component among women who were not frail. Among women in the WIHS who are in their mid-fifties, we found an overall frailty prevalence and a one-year risk of frailty that were comparable to estimates from women in the general population who are at least 65 years old. Our findings suggest that social and behavioral risk factors that promote aging could play a pivotal role in frailty occurrence among women who are currently living with HIV or at risk for HIV. Future studies should investigate modifiable risk factors to reduce the burden of frailty among women with and at risk for HIV, who are vulnerable to frailty at ages even younger than 65.

Table 2. Baseline Characteristics of Women's Interagency HIV Study Participants, 2015-2017.

Characteristic		Prevalence Sample (n=1,404)				One-Year Incidence Sample (n=378)			
		HIV+ (n=1,025)		HIV- (n=379)		HIV+ (n=277)		HIV- (n=101)	
		N	%	N	%	N	%	N	%
Age (years)	40-44	133	13.0	54	14.3	31	11.2	26	25.7
	45-49	222	21.7	95	25.1	72	26.0	27	26.7
	50-54	289	28.2	87	23.0	71	25.6	16	15.8
	55-59	210	20.5	69	18.2	61	22.0	13	12.9
	60-84	171	16.7	74	19.5	42	15.2	19	18.8
Region[a]	Midwest	164	16.0	62	16.4	74	26.7	38	37.6
	Northeast	328	32.0	113	29.8	80	28.9	19	18.8
	South	386	37.7	139	36.7	75	27.1	23	22.8
	West	147	14.3	65	17.2	48	17.3	21	20.8
Race/Ethnicity									
	White Non-Hispanic	128	12.5	27	7.1	40	14.4	10	9.9
	Black Non-Hispanic	761	74.2	294	77.6	209	75.4	77	76.2
	Other Non-Hispanic	34	3.3	24	6.3	10	3.6	7	6.9
	Hispanic	102	10.0	34	9.0	18	6.5	7	6.9
Education	< High School	316	30.9	110	29.0	81	29.4	22	21.8
	High School	334	32.6	115	30.3	91	33.0	28	27.7
	> High School	374	36.5	154	40.6	104	37.7	51	50.5
	Unknown	1		0		1		0	
Annual Household Income	≤ $6,000	137	13.4	78	20.7	37	13.4	24	23.8
	$6,001-$12,000	356	34.8	112	29.8	103	37.2	19	18.8
	$12,001-$18,000	145	14.2	48	12.8	31	11.2	12	11.9
	$18,001-$24,000	105	10.3	26	6.9	20	7.2	11	10.9
	> $24,000	279	27.3	112	29.8	86	31.1	35	34.7

	Unknown	3		3		0		0	
Smoking	Never Smoker	355	34.6	97	25.6	99	35.7	28	27.7
	Former Smoker	278	27.1	105	27.7	65	23.5	32	31.7
	Current Smoker	392	38.2	177	46.7	113	40.8	41	40.6
Alcohol Use (drinks/week)	0	589	57.5	170	44.9	148	53.4	48	47.5
	0.1-7	371	36.2	136	35.9	103	37.2	35	34.7
	7.1-12	24	2.3	29	7.7	6	2.2	3	3.0
	> 12	41	4.0	44	11.6	20	7.2	15	14.9
Other Substance Use[b]	Yes	252	24.6	128	33.8	60	21.7	31	30.7
Active Hepatitis C Infection	RNA+	96	9.4	21	5.5	33	12.0	5	5.0
	Unknown	2				1			
HIV-specific characteristics									
CD4 Count (cells/mm^3)[c]		652 (441, 867)				640 (436, 873)			
HIV Viral Load (copies/mL)[c,d]		20 (20, 29)				20 (20, 20)			

Abbreviations: WIHS, Women's Interagency HIV Study

[a]Site categorization: Midwest (Chicago, IL), Northeast (Brooklyn, NY; Washington, DC), South (Atlanta, GA; Chapel Hill, NC; Miami, FL; Birmingham, AL/Jackson, MS), West (San Francisco/Bay Area, CA)

[b] Substance use: crack cocaine, cocaine, heroin, methadone, methamphetamines, amphetamines, marijuana, prescription drug abuse, or other recreational drug use

[c]Median (interquartile range)

[d]Lower limit of detection is 20 copies/mL

Figure 5. Prevalence of Frailty in the Women's Interagency HIV Study by HIV Status and Age, 2015-2017 (n=1,404).

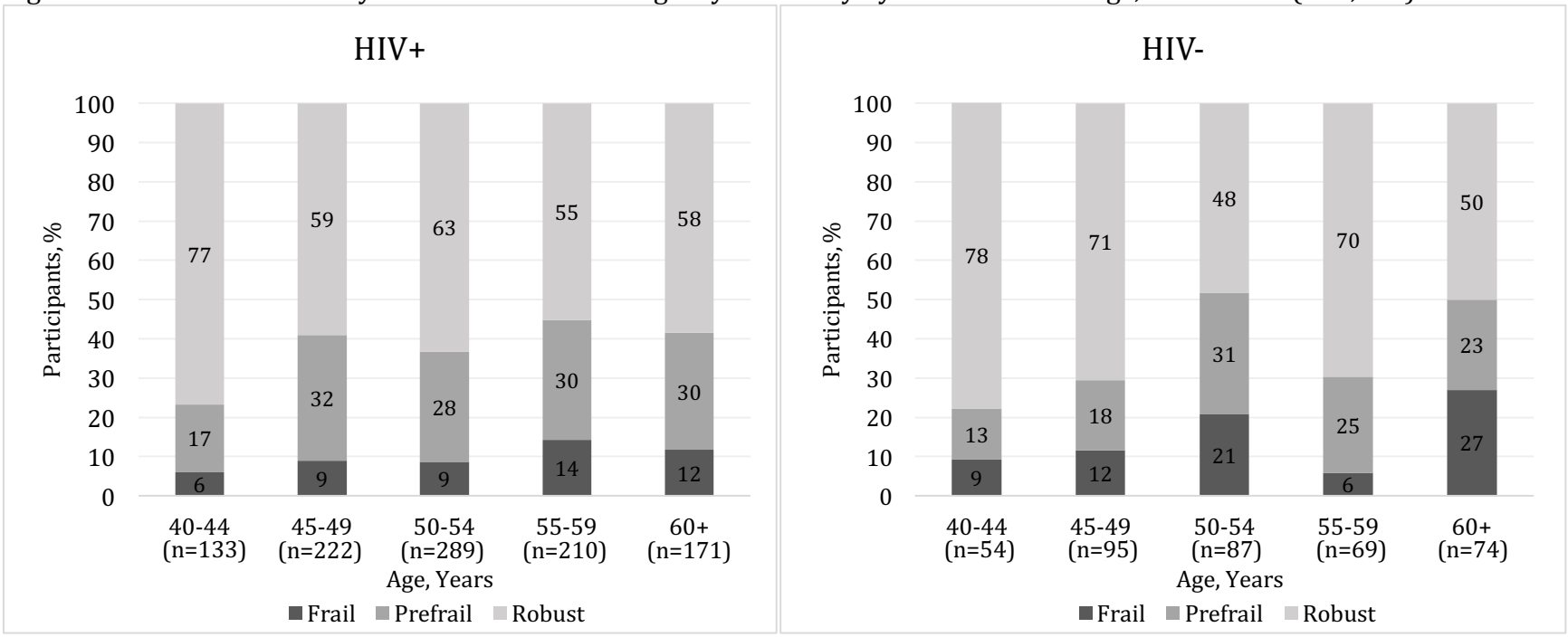
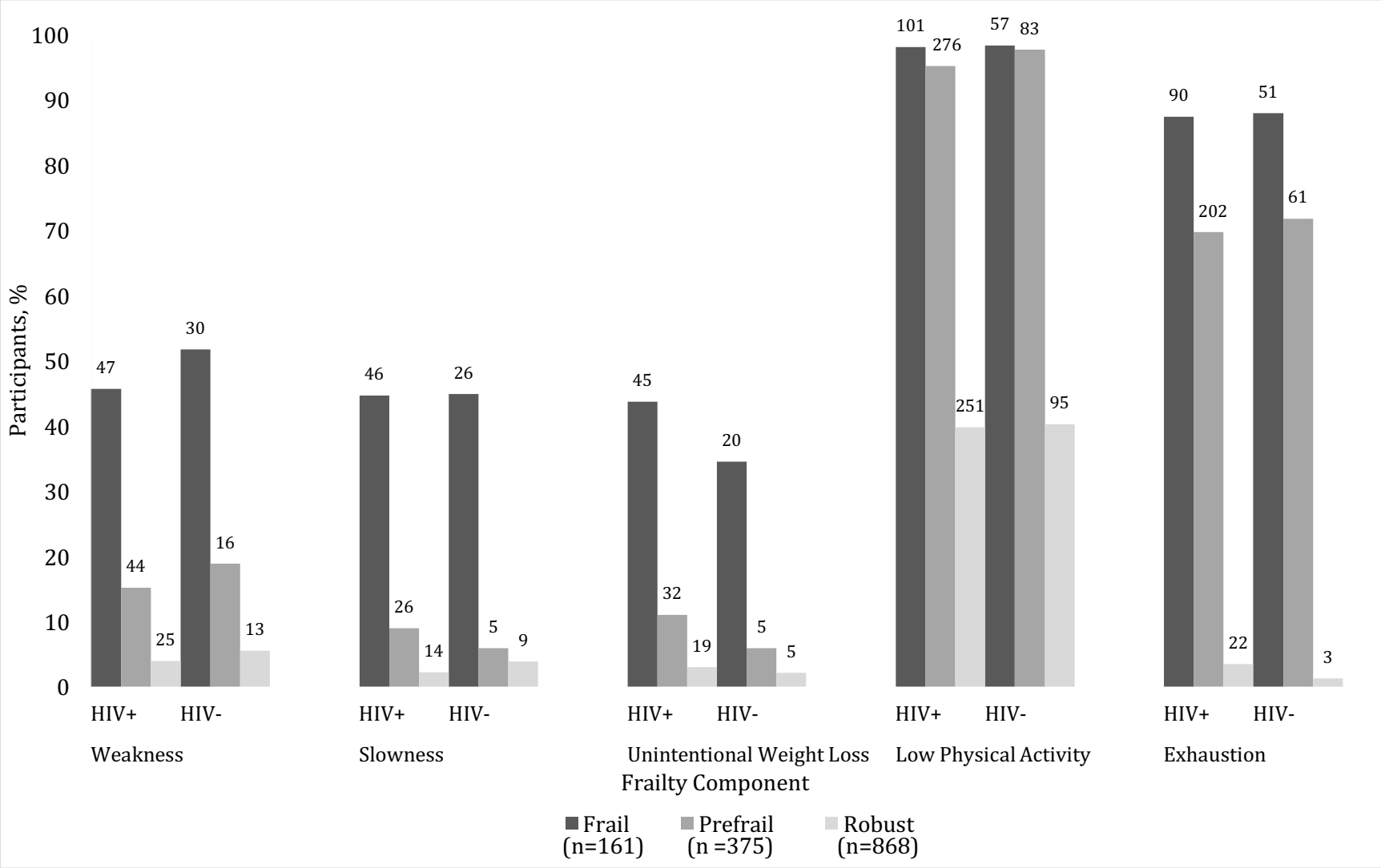
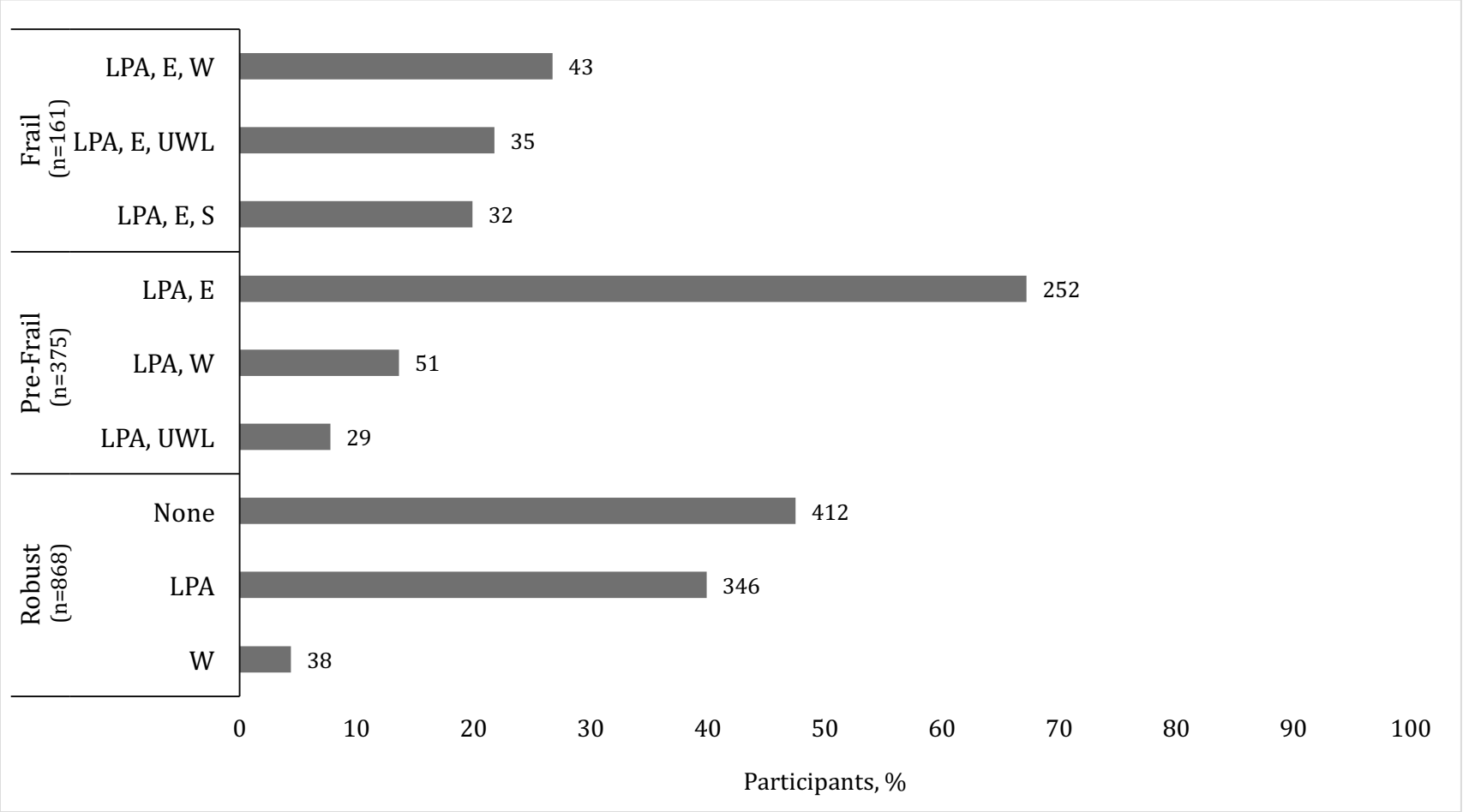


Figure 6. Distribution of Frailty Components among Prevalence Sample in the Women's Interagency HIV Study by Frailty Status and HIV Status 2015-2017 (n=1,404).



Note. The height of each bar represents the percentage of participants and the value above each bar represents the number of participants.

Figure 7. Most Common Combinations of Frailty Components among Prevalence Sample in the Women's Interagency HIV Study by Frailty Status, 2015-2017 (n=1,404).



Abbreviations: E, Exhaustion; LPA, Low Physical Activity; S, Slowness; UWL, Unintentional Weight Loss; W, Weakness

Note. The length of each represents the percentage of participants and the value adjacent to each bar represents the number of participants

Figure 8. Severity of Low Physical Activity and Exhaustion among Prevalence Sample in the Women's Interagency HIV Study by Frailty Status, 2015-2017 (n=1,404).

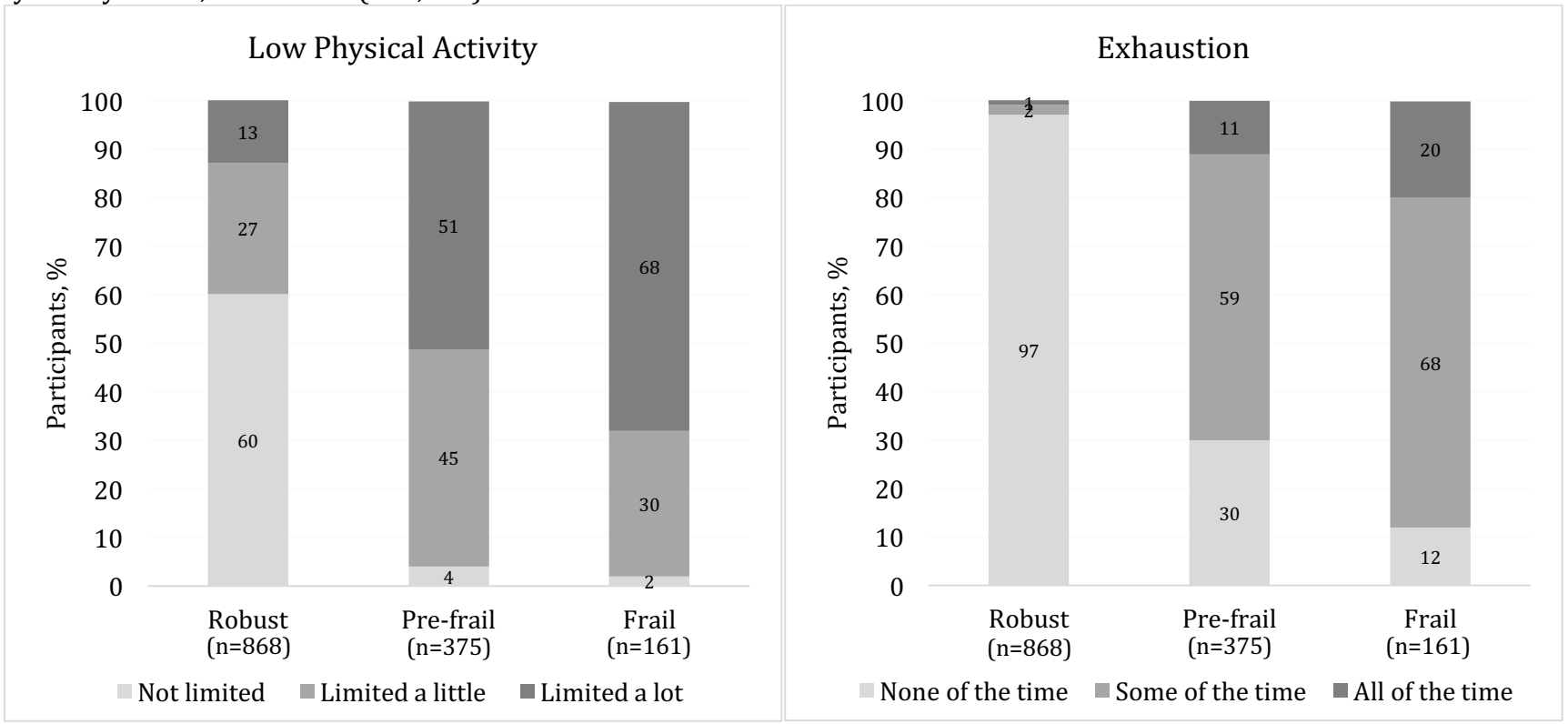


Table 3. One-Year Crude and Age-Adjusted Risk Ratio and Risk Difference for Frailty in the Women's Interagency HIV Study, 2015-2017.

	N	Cases	Crude Risk % (95% CI)	Crude RR (95% CI)	Crude RD (95% CI)	Age-Adjusted RR (95% CI)	Age-Adjusted RD[a] (95% CI)
One-Year							
Overall	378	25	6.61 (4.11, 9.12)	-		-	-
HIV-	101	7	6.93 (1.98, 11.88)	1.00	0.00	1.00	0.00
HIV+	277	18	6.50 (3.60, 9.40)	0.94 (0.40, 2.18)	0.00 (-0.06, 0.05)	0.91 (0.39, 2.10)	-0.03 (-0.09, 0.03)

Abbreviations: CI, Confidence Interval; RD, Risk Difference; RR, Risk Ratio

[a]Age (continuous variable)

CHAPTER 5. EFFECT OF SMOKING ON THE ONE-YEAR RISK OF FRAILTY

Introduction

It is well established that cigarette smoking is a cause of premature death and disease[45, 46]. Smoking is the cause of many chronic diseases associated with aging, including cardiovascular disease, respiratory disease, and cancer[45, 46]. Evidence suggests there may be a link between smoking and frailty, a syndrome of physical weakness that is associated with higher risks of hospitalization, institutionalization, and premature death[19, 38, 41, 44, 65]. Cross-sectional studies have reported higher frailty prevalence in smokers than in non-smokers, among those 65 years and older[25, 38, 44]. Limited longitudinal data on smoking and frailty have suggested that smoking is a risk factor for incident frailty in the general population[25, 43].

Smoking is more common among people with HIV than in the general population[49]. One nationally representative study in 2009 among over 30,000 US adults from the Medical Monitoring Project and National Health Interview Survey estimated that while smoking prevalence was 21% among US adults in the general population, it was 42% among people with HIV receiving medical care[49]. People with HIV who smoke are at increased risks for some HIV-related and non-HIV-related conditions compared to people with HIV who do not smoke, including bacterial pneumonia, lung cancer, and chronic obstructive pulmonary disease[51-54]. It is presumed that one pathway by which smoking and HIV infection can

cause increases risk for some aging-related diseases is through their independent associations with increased levels of inflammatory markers[54]. Thus it is plausible that some of the same mechanisms by which smoking causes aging-related disease among people with HIV, such as increased inflammation, could similarly result in an increased risk of frailty among those with smoking exposure in this population[53, 54].

Older adults, people with HIV, women, racial/ethnic minorities, and those with low socioeconomic status (SES) are more likely to be frail[24, 25, 38, 41, 66]. Our previous study reported that estimates for frailty prevalence and incidence among women with and at risk for HIV infection, who were on average 52 years old, were comparable to those from the general population at least 65 years old. Smoking is a modifiable risk factor and its elimination could substantially reduce frailty in populations where smoking is highly prevalent, such as people with HIV. To our knowledge, there are no US studies estimating the independent effect of smoking on incident frailty. Thus the effect of smoking on frailty risk also remains unknown for people with HIV, and for those younger than 65.

In this study, we sought to estimate the effect of smoking on the one-year risk of frailty among women with and at risk for HIV infection. We hypothesized that the risk of frailty would be higher for women with smoking exposure compared to women without smoking exposure. We also investigated whether the effect of smoking exposure would be more pronounced among women with HIV than in women at risk for HIV infection, since evidence suggests that the effect of smoking on some aging-related diseases is greater among people with HIV than in people without HIV.

Methods

Study Sample

The Women's Interagency HIV Study (WIHS) is a multisite, prospective cohort of women with or at risk for HIV designed to characterize the progression of HIV infection in women [55]. This study included data from eight WIHS sites located in Brooklyn, NY; San Francisco, CA; Chicago, IL; Washington, DC; Atlanta, GA; Chapel Hill, NC; Miami, FL; and Birmingham, AL/Jackson, MS[55-57]. Institutional review board approval was obtained at each site and written informed consent was obtained from all women. At semiannual follow-up visits, the WIHS collects a wide range of data, including demographic and psychosocial characteristics[55-57]. Methods have been described in detail elsewhere[55-57]. This analysis was restricted to women $\geq$ 40 years who had two frailty assessments taken over approximately a one-year period of follow-up between October 1, 2015 and September 30, 2017. Women with missing data were considered incomplete cases and excluded (Appendix Figure 1). Overall, 424 women had two frailty assessments taken approximately a year apart during this study period. Of these 424 women, 46 were excluded due to frail status at the baseline visit and 1 was excluded due to missing data on income. This resulted in a final sample of 377 women for whom data was analyzed to estimate the effect of smoking exposure on the one-year risk of frailty.

Outcome definition

Starting on October 1, 2015, the WIHS protocol has included the measurement of frailty components and assigned frailty status among women who are 40 years of age and older. The Fried Frailty Index (henceforth, FFI), a tool validated in the Cardiovascular

Health Study (CHS), is used to operationalize the frailty phenotype based on five components: weakness, slowness, unintentional weight loss, low activity, and exhaustion[24]. Frail status was defined as exceeding the component-specific threshold (Table 1) for at least three frailty components, pre-frail status was defined as exceeding the threshold for two frailty components, and robust status was defined as exceeding the threshold for no more than one frailty component[24]. As in the CHS, two performance-based measures, grip strength and walking speed, operationalized the FFI components of weakness and slowness. Grip strength was measured by squeezing a Jamar dynamometer with maximum force using the dominant hand, and the highest value (greatest strength) of three attempts was used for analysis. Walking speed was measured in seconds by a timed four-meter walk, and the fastest time of two attempts was used for analysis. Three ongoing, prospectively collected, self-reported measures in the WIHS operationalized the FFI components of unintentional weight loss, low activity, and exhaustion[38].

Performance-based measures were assessed at least every other semiannual visit. Exhaustion and low physical activity were assessed at every other semiannual visit and unintentional weight loss was assessed at each semiannual visit. The two most recent performance-based measurements were used to estimate the one-year risk of frailty. If any of the self-reported frailty components were missing, the closest previous or subsequent value that occurred within two visits of each performance-based measurement was used.

Exposure Definition and Covariates

There were two primary exposures in this study which included current cigarette smoking status (smoker or non-smoker) and the number of cigarette smoking pack-years

at the baseline visit. At each semiannual visit, women self-report smoking status, with women classified as current smokers if they answer "yes" to the following question: "Since your study visit on…have you smoked cigarettes?" Additional smoking data are collected at each semiannual visit and smoking pack-years were determined based on participants' self-reported average number of cigarettes or packs smoked per day. To calculate the number of smoking pack-years, the number of packs smoked per day was averaged across all visits with non-missing values and was multiplied by the number of years having smoked.

The following covariates were determined at the baseline visit and utilized as confounders: age (40-84 years), race/ethnicity (black non-Hispanic, all other races/ethnicities), education (<high school, high school, and >high school), annual household income (≤12,000, >$12,000), region (Midwest, Northeast, South, and West), heavy weekly alcohol use (≤7 drinks, >7 drinks), and any other recreational drug use (yes, no). If any exposure or covariate values were missing at the baseline visit, the last reported values were used.

Statistical Analysis

Participant characteristics were summarized according to current smoking status using percent or median with interquartile range (IQR), as appropriate. Potential confounders were hypothesized from the literature and identified using a directed acyclic graph (Appendix Figure 2)[58]. Stabilized inverse-probability-of-treatment weights were used to produce estimates for the one-year risk of frailty comparing current smokers to non-smokers, and were constructed using two logistic regression models. The first model

estimated the unconditional probability of being a current cigarette smoker, and the second model estimated the probability of being a current cigarette smoker conditional on measured covariates. The final stabilized weight for the exposed was the marginal probability of being a current cigarette smoker divided by the participant's conditional probability of being a current cigarette smoker. The final stabilized weight for the unexposed was the marginal probability of not being a current cigarette smoker divided by the participant's conditional probability of not being a current cigarette smoker. Key confounders were chosen to be included in the most parsimonious final weighted (adjusted) models if they were associated with the exposure in the conditional logistic regression model ($p<0.05$). A weighted log-binomial model was used to estimate multivariable-adjusted risk ratios (RR) for the one-year risk of frailty comparing current smokers to non-smokers. A weighted linear-binomial model was used to estimate multivariable-adjusted risk differences (RD) for the one-year risk of frailty comparing current smokers to non-smokers. Confidence intervals (CIs) were based on the robust (Huber-White) variance estimator. Smoking pack-years was categorized into quintiles to relax linearity assumptions. The two highest quintiles of the exposure distribution demonstrated a similar magnitude of effect on the one-year risk of frailty and were chosen as the cutoff for the final contrast comparing high to low cumulative smoking exposure in pack-years (>7.5, ≥7.5). As described above, inverse-probability-of-treatment weights were similarly constructed to produce weighted log-binomial and linear-binomial models estimating the one-year risk of frailty comparing women whose cumulative smoking exposure was more than 7.5 pack-years to women whose cumulative smoking exposure was less than or equal to 7.5 pack-years, after adjustment for key confounders. As a

sensitivity analysis, we compared our results with those using an alternate definition for smoking pack-years. If the self-reported average number of cigarettes or packs smoked per day at any semiannual visit was missing, the previous non-missing value was carried forward until it was replaced by the next non-missing value. To calculate the number of smoking pack-years using the alternate definition, the number of packs smoked per day across each visit was averaged and multiplied by the number of years having smoked. Data analyses were performed using SAS software version 9.3 (SAS Institute Inc., Cary, NC).

Results

Baseline characteristics of the sample participants are presented in Table 4. The median age was 53 years (IQR: 48-58). The majority of women were black non-Hispanic (76%). Current non-smokers were more likely to have an annual household income greater than $12,000 (64% vs. 33%) and at least a high school education (80% vs. 63%). The overall prevalences of heavy weekly alcohol use and any other recreational drug use were 12% and 24%, respectively, with heavy weekly alcohol use and any other recreational drug use more common among current smokers.

Overall, the one-year risk of frailty was 6.6% (n=25/377). Table 5 presents the crude and adjusted RRs and RDs for the one-year risk of frailty comparing current smokers to non-smokers. In unadjusted analyses, current smokers were more likely to become frail compared to non-smokers (crude RR = 2.20; 95% CI: 1.01, 4.76). After adjustment for confounding, including any other recreational drug use, this effect was attenuated, such that current smokers were 1.68 times as likely to become frail compared to current non-smokers (95% CI: 0.69, 4.06). After adjustment for confounding, results were similar when

adjusting only for heroin, crack, cocaine, or injection drug use rather than any other recreational drug use (RR = 1.61; 95% CI: 0.64, 4.03).

Table 6 presents the crude and adjusted RRs and RDs for the one-year risk of frailty comparing cumulative smoking exposure in pack-years. For each five-unit increase in smoking pack-years, women were 1.15 times as likely to become frail (95% CI: 1.01, 1.31). The median (IQR) of smoking pack-years for each quintile was 0.0 (0.0-0.0), 0.4 (0.2, 0.8), 4.3 (2.7, 6.0), 10.3 (8.8, 12.9), and 21.8 (18.0-28.9). After adjustment for confounding, women who smoked at least 7.5 pack-years were 2.72 times as likely to become frail than women who smoked less than 7.5 pack-years (95% CI: 0.96, 7.67). After adjustment for confounding, the effect was more pronounced when adjusting only for heroin, crack, cocaine, or injection drug use rather than any other recreational drug use (RR = 3.22; 95% CI: 1.17, 8.86).

In restricting analyses to women with HIV only (Table 7), this effect also appeared to be more pronounced; women whose cumulative smoking exposure was at least 7.5 pack-years were 4.10 times as likely to become frail over the one-year follow-up period than women whose cumulative smoking exposure was less than 7.5 pack-years (95% CI: 1.22, 13.78). In sensitivity analyses, results were qualitatively similar when using the alternate definition for calculating smoking pack-years (Table 8).

Discussion

We demonstrated that reported cigarette smoking increased the one-year risk of frailty in this sample of US women with and at risk for HIV infection. Our results suggest that women who reported higher levels of cumulative exposure to smoking, reflected by a

higher number of smoking pack-years, are at an increased risk for frailty. This latter effect could be more pronounced among women with HIV. These results persisted after adjustment for confounding factors including heavy alcohol use and recreational drug use.

A sample of over 40,000 women in the US general population aged 65 and older, reported that the unadjusted odds ratio for developing frailty over a three-year period for current smokers and former smokers compared to never smokers was 2.90 (95% CI: 2.35, 3.57) and 1.12 (95% CI: 1.02, 1.23), respectively[25]. Though there are no US studies estimating the independent effect of smoking on frailty risk, one recent longitudinal study among a nationally representative sample of 2,542 adults aged 60 and older in England found that current smokers were 2.07 times (95% CI: 1.39, 3.39) as likely to develop frailty over four years of follow-up compared to non-smokers, adjusting for age and gender[43]. This effect was attenuated to 1.60 (95% CI: 1.02, 2.51) after adjustment for age, gender, SES, alcohol use, cognitive function and loneliness[43]. In our US study population of women with and at risk for HIV infection, our results estimating the independent effect of current smoking status on frailty risk were comparable to the previous study among the English general population of those aged 60 and older[43].

In the US general population, substance use is more common among smokers than non-smokers[67]. However, the independent effect of substance use on the risk of frailty remains unknown. One study found that the co-occurrence of injection drug use and hepatitis C infection was associated with DNA methylation signatures that were reflective of a higher degree of frailty among HIV-infected men[61]. In our study population, recreational drug use was more prevalent than in the US general population[68]. To ensure comparability to HIV-seropositive women, HIV-seronegative women with HIV-related risk

characteristics, such as injection drug use, were targeted for recruitment into the WIHS[55]. Thus, in our study results were presented with and without adjustment for recreational drug use. After additional adjustment for this factor we observed a similar magnitude of effect as the previous study among the English population comparing the risk of frailty between current smokers and non-smokers [43].

Smoking was also assessed in pack-years, which is one way to measure cumulative exposure to smoking. Research shows that this measure can be useful in accounting for both the duration and intensity of smoking, details that are lost when using current smoking status alone [69, 70]. We observed a more pronounced effect when assessing the effect of cumulative smoking exposure using smoking pack-years. After adjustment for confounding factors, we demonstrated that a higher number of smoking pack-years was associated with an increased one-year risk of frailty. In our study population, current smokers had higher levels of cumulative smoking exposure (median [IQR] for smoking pack-years: 12.4 [8.0-19.2]) compared to former smokers (median[IQR] for smoking pack-years: 4.2 [1.2-9.8]). Given that the effect was more pronounced when considering cumulative smoking exposure, results suggest that in addition to current smoking exposure, the intensity and duration of smoking exposure may play a pivotal role in frailty development.

There are several mechanisms through which smoking can cause a variety of aging-related diseases; these mechanisms include increased levels of inflammatory markers and enhanced oxidative stress[48, 71]. Among men and women in the English Longitudinal Study of Aging, one study found that higher levels of C-reactive protein and fibrinogen were associated with increased frailty risk among women but not among men, and persisted

after adjustment for confounding factors including current smoking status[72]. People with HIV have higher levels of some inflammatory markers independent of smoking, even among those who are virally suppressed[73, 74]. In our study, the effect of cumulative smoking exposure on frailty risk was more apparent among women with HIV. Given previous evidence[48, 71-74], it is plausible that the combination of smoking exposure and HIV infection on inflammatory processes could contribute to an increased risk of frailty among this population.

There are some limitations to our study. First, some women had incomplete data on all five frailty components at both the baseline visit and the follow-up visit over the one-year period (Appendix Table 2). However, among women with at least one frailty assessment during this study period, the distributions for current smoking exposure (n=[569/1404]= 41%) and frailty (n=[161/1404]=11%) were similar to the baseline distributions among those women with two frailty assessments, which were 41% (n=172/424) and 11% (n=46/424), respectively. Second, though identification of potential confounders was informed by a DAG and final selection was determined by a conditional regression model, it is possible that unmeasured confounding could help explain our results. Third, frailty can be episodic in the short-term. However, our study sought to assess whether smoking could have an effect on frailty even over a relatively short period of follow-up. Our results were also consistent with the limited number of prospective studies reporting that exposure to cigarette smoking is a risk factor for frailty over longer periods of follow-up. Future studies are needed to assess the long-term impacts of various levels of smoking exposure as a cause of frailty among women with and at risk for HIV infection. Lastly, the RR and RD estimating the risk of frailty were imprecise. However, our observed

magnitudes of effect were similar to those from the previous longitudinal study among English adults in the general population comparing the four-year risk of frailty between current smokers and non-smokers[43]. Our results were also robust to using two separate measures of exposure to smoking, which included current smoking status and smoking pack-years. The pattern of increased frailty risk for higher levels of smoking exposure was consistent.

This study demonstrated that smoking is independently associated with an increased frailty risk, even over a one-year period of follow-up, among women with and at risk for HIV infection who are younger than 65 years of age. This study gives weight to evidence that smoking is an independent risk factor for frailty, and suggests that the intensity and duration of smoking could play a crucial role in frailty development, rather than current smoking alone. Future studies are needed to determine the long-term effects of various levels of smoking on the risk of frailty, and the impact that targeted smoking interventions could have in reducing frailty among women with and without HIV infection.

Table 4. Baseline Characteristics of Sample Participants by Current Smoking Status in the Women's Interagency HIV Study, 2015-2017.

Characteristic		Non-Smoker (n=224)		Smoker (n=153)		Overall (n=377)	
		N	%	N	%	N	%
Age (years)[a]		53 (48-58)		52 (48-59)		53 (48-58)	
Region[b]	Midwest	49	21.9	63	41.2	112	29.7
	Northeast	74	33.0	24	15.7	98	26.0
	South	64	28.6	34	22.2	98	26.0
	West	37	16.5	32	20.9	69	18.3
HIV Status	Negative	60	26.8	41	26.8	101	26.8
	Positive	164	73.2	112	73.2	276	73.2
Race/Ethnicity	Black Non-Hispanic	158	70.5	128	83.7	286	75.9
	All Other Races	66	29.5	25	16.3	91	24.1
Education	<High School	46	20.5	57	37.3	103	27.3
	High School	67	29.9	52	34.0	119	31.6
	>High School	111	49.6	44	28.8	155	41.1
Annual Household Income	≤$12,000	81	36.2	102	66.7	194	51.5
	>$12,000	143	63.8	51	33.3	183	48.5
Alcohol Use (drinks/week)	≤7	205	91.5	126	82.4	331	87.8
	>7	19	8.5	27	17.7	46	12.2
Any Other Recreational Drug Use[c]	Yes	29	13.0	62	40.5	91	24.1

Abbreviations: WIHS, Women's Interagency HIV Study

[a]Median (interquartile range)

[b]Site categorization: Midwest (Chicago, IL), Northeast (Brooklyn, NY; Washington, DC), South (Atlanta, GA; Chapel Hill, NC; Miami, FL; Birmingham, AL/Jackson, MS), West (San Francisco, CA)

[c]Any other recreational drug use: crack cocaine, cocaine, heroin, methadone, methamphetamines, amphetamines, marijuana, prescription drug abuse, or other recreational drug use

Table 5. One-Year Crude and Adjusted Risk Ratios and Risk Differences for Frailty by Current Smoking Status in the Women's Interagency HIV Study Using Stabilized Inverse-Probability-of-Treatment Weighting, 2015-2017 (n=377).

Model		RR (95% CI)	RD (95% CI)	Mean (Range) of Stabilized Weights
Crude				-
	Non-smoker	1.00	0.00	
	Smoker	2.20 (1.01, 4.76)	0.05 (0.00, 0.11)	
Fully-Adjusted[a]				1.00 (0.46, 4.89)
	Non-smoker	1.00	0.00	
	Smoker	2.04 (0.85, 4.87)	0.05 (-0.02, 0.11)	
Fully-Adjusted[b]				1.02 (0.42, 11.08)
	Non-smoker	1.00	0.00	
	Smoker	1.61 (0.64, 4.03)	0.03 (-0.03, 0.09)	
Fully-Adjusted[c]				1.01 (0.43, 10.16)
	Non-smoker	1.00	0.00	
	Smoker	1.68 (0.69, 4.06)	0.03 (-0.02, 0.09)	

Abbreviations: RR, Risk Ratio; CI, Confidence Interval; RD, Risk Difference

[a]Weighted model adjusts for age (continuous), education, heavy alcohol use, income, race, region

[b]Weighted model adjusts for age (continuous), education, heavy alcohol use, income, limited recreational drug use ((injection drug use, or use of heroin, crack, cocaine), none), race, region

[c]Weighted model adjusts for age (continuous), education, heavy alcohol use, income, any other recreational drug use (crack cocaine, cocaine, heroin, methadone, methamphetamines, amphetamines, marijuana, prescription drug abuse, or other recreational drug use), none), race, region

Table 6. One-Year Crude and Adjusted Risk Ratios and Risk Differences for Frailty by Cigarette Smoking Pack-Years in the Women's Interagency HIV Study Using Stabilized Inverse-Probability-of-Treatment Weighting, 2015-2017 (n=377).

Model		Cases	N	RR (95% CI)	RD (95% CI)	Mean (Range) of Stabilized Weights
Crude (Linear)						
Continuous (5-unit increment)		25	377	1.15 (1.01, 1.31)	0.01 (0.00, 0.03)	-
Quintiles (1-unit increment)		25	377	1.29 (0.99, 1.67)	0.01 (0.00, 0.03)	-
Crude (Categorical)						-
	≤7.5	8	226	1.00	0.00	
	>7.5	17	151	3.18 (1.41, 7.18)	0.08 (0.02, 0.13)	
Fully-Adjusted[a]						1.51 (0.45, 5.75)
	≤7.5	8	226	1.00	0.00	
	>7.5	17	151	2.86 (1.05, 7.78)	0.09 (0.01, 0.17)	
Fully-Adjusted[b]						1.57 (0.46, 7.38)
	≤7.5	8	226	1.00	0.00	
	>7.5	17	151	3.22 (1.17, 8.86)	0.11 (0.02, 0.19)	
Fully-Adjusted[c]						1.70 (0.47, 7.10)
	≤7.5	8	226	1.00	0.00	
	>7.5	17	151	2.72 (0.96, 7.67)	0.09 (0.00, 0.17)	

Abbreviations: RR, Risk Ratio; CI, Confidence Interval; RD, Risk Difference

[a]Weighted model adjusts for age (continuous), education, heavy alcohol use, income, race, region

[b]Weighted model adjusts for age (continuous), education, heavy alcohol use, income, limited recreational drug use ((injection drug use, or use of heroin, crack, cocaine), none), race, region

[c]Weighted model adjusts for age (continuous), education, heavy alcohol use, income, any other recreational drug use (crack cocaine, cocaine, heroin, methadone, methamphetamines, amphetamines, marijuana, prescription drug abuse, or other recreational drug use), none), race, region

Table 7. One-Year Crude and Adjusted Risk Ratios and Risk Differences for Frailty by Cigarette Smoking Pack-Years *Among Women with HIV* in the Women's Interagency HIV Study Using Stabilized Inverse-Probability-of-Treatment Weighting, 2015-2017 (n=276).

Model		Cases	N	RR (95% CI)	RD (95% CI)	Mean (Range) of Stabilized Weights
Crude (Linear)						
Continuous (5-unit increment)		18	276	1.21 (1.03, 1.43)	0.02 (0.00, 0.04)	-
Quintiles (1-unit increment)		18	276	1.34 (0.99, 1.82)	0.01 (0.00, 0.03)	-
Crude (Categorical)						-
	≤7.5	6	169	1.00	0.00	
	>7.5	12	107	3.16 (1.22, 8.16)	0.08 (0.01, 0.14)	
Fully-Adjusted[a]						1.54 (0.46, 6.64)
	≤7.5	6	169	1.00	0.00	
	>7.5	12	107	4.32 (1.39, 13.42)	0.13 (0.02, 0.23)	
Fully-Adjusted[b]						1.75 (043, 19.19)
	≤7.5	6	169	1.00	0.00	
	>7.5	12	107	4.90 (1.49, 16.08)	0.15 (0.01, 0.29)	
Fully-Adjusted[c]						1.84 (0.45, 11.43)
	≤7.5	6	169	1.00	0.00	
	>7.5	12	107	4.10 (1.22, 13.78)	0.12 (0.01, 0.23)	

Abbreviations: RR, Risk Ratio; CI, Confidence Interval; RD, Risk Difference

[a]Weighted model adjusts for age (continuous), education, heavy alcohol use, income, race, region

[b]Weighted model adjusts for age (continuous), education, heavy alcohol use, income, limited recreational drug use ((injection drug use, or use of heroin, crack, cocaine), none), race, region

[c]Weighted model adjusts for age (continuous), education, heavy alcohol use, income, any other recreational drug use (crack cocaine, cocaine, heroin, methadone, methamphetamines, amphetamines, marijuana, prescription drug abuse, or other recreational drug use), none), race, region

Table 8. One-Year Crude and Adjusted Risk Ratios and Risk Differences for Frailty by Cigarette Smoking Pack-Years Using Alternate Definition in the Women's Interagency HIV Study and Stabilized Inverse-Probability-of-Treatment Weighting, 2015-2017 (n=377).

Model		Cases	N	RR (95% CI)	RD (95% CI)	Mean (Range) of Stabilized Weights
Crude (Linear)						
Continuous (5-unit increment)		25	377	1.15 (1.01, 1.30)	0.01 (0.00, 0.03)	-
Quintiles (1-unit increment)		25	377	1.26 (0.98, 1.64)	0.01 (0.00, 0.03)	-
Crude (Categorical)						-
	≤7.5	9	226	1.00	0.00	
	>7.5	16	151	2.66 (1.21, 5.86)	0.07 (0.01, 0.12)	
Fully-Adjusted[a]						1.45 (0.47, 5.02)
	≤7.5	9	226	1.00	0.00	
	>7.5	16	151	2.90 (1.11, 7.55)	0.09 (0.01, 0.17)	
Fully-Adjusted[b]						1.53 (0.46, 8.08)
	≤7.5	9	226	1.00	0.00	
	>7.5	16	151	3.32 (1.25, 8.80)	0.11 (0.02, 0.20)	
Fully-Adjusted[c]						1.64 (0.48, 6.26)
	≤7.5	9	226	1.00	0.00	
	>7.5	16	151	2.80 (1.04, 7.56)	0.09 (0.01, 0.17)	

Abbreviations: RR, Risk Ratio; CI, Confidence Interval; RD, Risk Difference

[a]Weighted model adjusts for age (continuous), education, heavy alcohol use, income, race, region

[b]Weighted model adjusts for age (continuous), education, heavy alcohol use, income, limited recreational drug use ((injection drug use, or use of heroin, crack, cocaine), none), race, region

[c]Weighted model adjusts for age (continuous), education, heavy alcohol use, income, any other recreational drug use (crack cocaine, cocaine, heroin, methadone, methamphetamines, amphetamines, marijuana, prescription drug abuse, or other recreational drug use), none), race, region

CHAPTER 6. CONCLUSION

SUMMARY OF FINDINGS

This project sought to estimate the prevalence and one-year risk of frailty, and examine the effect of cigarette smoking on the one-year risk of frailty among a US cohort of women with and at-risk for HIV infection who were at least 40 years of age. In summary, we demonstrated that the prevalence and one-year risk of frailty among women in their mid-fifties with and at risk for HIV was comparable to women in the general population who are at least 65 years of age. Our findings also indicated that reported exposure to cigarette smoking increased the risk for frailty among women with and at risk HIV infection.

For aim one, we showed that the prevalence of frailty in this US sample of women with and at risk for HIV was 11.5% (10% for HIV+; 15% for HIV-). After validating the FFI, the CHS estimated baseline frailty prevalence among adults in the general population aged 65 and older was 7% among women and 5% among men[24]. Another study among a representative sample of Medicare enrollees aged 65 in the National Health and Aging Trends Study estimated frailty prevalence using the FFI was 17% among women and 13% among men[31]. Lastly, a previous analysis in the WIHS using data from 2005, estimated frailty prevalence using the FFI was 17% among women with HIV and 10% among women at risk for HIV[38]. However, in contrast to the two previous studies using the FFI, we chose

to use the cut points for grip strength and walking speed that were validated in the general population by Fried, rather than using the highest and lowest quintiles of the distributions from our HIV-seronegative population[38] or the population distribution[31] for walking speed and grip strength, respectively. This approach allowed us to compare the performance on frailty measures of the WIHS population to the CHS population of women who were at least 65 years of age (11% vs. 7%)[24].

We also showed that the prevalence and distribution of frailty components among the frail, pre-frail, and robust were comparable for women with and at risk for HIV. The most common frailty components were low physical activity and exhaustion, which the prevalence among frail women was 98% and 88%, respectively. The previous study among older adults in Australia receiving rehabilitation and aged care services, found that low physical activity and exhaustion were also the most common frailty components at 65% and 63%[33]. We also determined that the most common combinations of frailty components for both pre-frail and frail women included low physical activity and exhaustion.

For aim two, the one-year risk of frailty was 6.6% (95% CI: 4.1, 9.1), and risks were similar for women with and at risk for HIV. The original study validating the FFI in the CHS, estimated that the four-year risk of frailty among men and women in the general population aged 65 and older was 7%[24]. A nationally representative sample of women in the general population aged 65-79 in the WHI-OS reported the three-year risk of frailty was 15%[25]. Many risk factors that were associated with an increased three-year risk of frailty in the WHI-OS are more common in the WIHS cohort[25]. For example, the prevalence of women with an annual household income less than $20,000 was 14%, and these women

were 2.0 times as likely to become frail over a three-year period compared to women with an annual household income of $75,000 or more (95% CI: 1.6, 2.4)[25]. In our sample estimating the one-year risk of frailty among women with and at risk for HIV, 55% of women had an annual household income that was no more than $18,000.

For aim three, we revealed that reported exposure to cigarette smoking was associated with an increased one-year risk of frailty among women with and at risk for HIV. Though the sample was not large enough to detect a significant difference, current smokers were 1.68 times (95% CI: 0.69, 4.06) as likely to become frail over a one-year period compared to non-smokers, adjusting for confounding factors. Also, women with higher cumulative exposure to smoking, reflected by a higher number of smoking pack-years (>7.5, ≤7.5), demonstrated an increased one-year risk for frailty, adjusting for confounding factors, and this effect appeared to be more apparent among women with HIV (RR: 4.1; 95% CI: 1.2, 13.8). The recent longitudinal study among a nationally representative sample of 2,542 adults aged 60 and older in England found that current smokers were 1.60 times (95% CI: 1.02, 2.51) as likely to develop frailty over four years of follow-up compared to non-smokers, adjusting for other factors[43]. In our study population of women in their mid-fifties with and at risk for HIV infection, we also observed a similar magnitude of effect comparing smokers to non-smokers over a one-year period after adjustment for confounding factors.

LIMITATIONS

This project is not without limitations. Women with missing data for performance-based measures (grip strength and walking speed) were excluded from analyses. We did

seek to examine the assumption that these missing data were not related to frailty, HIV status, or smoking status. We examined the distributions of the other three frailty components that were adequately captured for women at least 40 years old during the study period. We found that the distributions for HIV status, smoking status, and the other three components among excluded women were similar to those of women included in our analyses. We also found the distributions for current smoking exposure and frailty for women with at least one frailty assessment during this study period were similar to the baseline distributions among those women with two frailty assessments. We also assessed the reasons women reported for not wanting to participate in any performance-based measurements. Among eligible women who declined to complete any performance-based measurements within the study period (n=126), 10% explicitly reported reasons related to inability, illness, or tiredness, and the distribution of HIV status was similar to those included in our study.

A second limitation of this project is that the period of follow-up was relatively short. Frailty can episodic in the short-term, but without intervention, transitions to a higher degree of frailty are more common and complete reversal from frailty to robustness is rare among elderly people[64]. It is worth noting that it is possible that variability in the short-term could result in misclassification of the outcome. However, there is no evidence to suggest that misclassification of frailty is likely to be differential with regard to smoking exposure. This project sought to assess whether smoking exposure could produce an effect on frailty even over a relatively short period of follow-up. Given the limited longitudinal data in frailty research, especially among people with HIV, it is still of interest to examine the effect of modifiable risk factors on the short-term risk of frailty among women with and

at risk for HIV that can help guide future research. Our results were also consistent with limited prospective studies in the general population reporting current cigarette smoking as a risk factor for frailty over longer periods of follow-up[43].

Also, estimates for the risk ratios and risk differences for frailty were imprecise. However, estimates for frailty prevalence and incidence were comparable between our population and the general population of women at least 65 years of age, and this pattern should be further examined. We also observed a similar magnitude of effect in our analyses to the previous longitudinal study in the general population comparing the four-year risk of frailty for current smokers and non-smokers[43]. Our results were also robust to using two separate measures of exposure to smoking, and the pattern of increased frailty risk for higher levels of reported exposure to smoking was consistent. Lastly, though identification of potential confounders was informed by a DAG and final selection was driven by a conditional regression model, it is possible that unmeasured confounding could help explain our results.

IMPLICATIONS AND FUTURE RESEARCH

Several characteristics associated with frailty in the general population are more prevalent among people with HIV[13, 49]. In addition to older age and female gender, minority race/ethnicity, lower SES, geographic location, comorbidities, poor nutrition, smoking, and possibly alcohol consumption are all characteristics associated with frailty [24, 31, 38, 39, 43]. As mentioned previously, people with HIV are more likely to smoke (42%) compared to the general population (21%)[49]. In our study population, many of these aging risk factors were highly prevalent among women with HIV, but some were even more

prevalent among women at risk for HIV. Thus, it is likely that the high burden of these aging risk factors among women with and at risk for HIV contributed to the high prevalence and risk of frailty in these populations relative to the general population. Future longitudinal studies are needed to pinpoint modifiable risk factors that will reduce frailty among populations vulnerable to frailty at ages younger than 65.

We also found that low physical activity and exhaustion were the most common frailty components and most commonly occurred in conjunction with each other among frail and pre-frail women with and at risk for HIV. The previous study among older adults in Australia receiving rehabilitation and aged care services, found that tailored interventions targeting identified characteristics of frailty reduced frailty and improved mobility over a 12-month period compared to usual care[33]. For example, one of the tailored interventions for frail adults with exhaustion included a referral to a psychiatrist. Previous studies also demonstrate that resistance exercise training increases strength in older adults, despite age-associated decreases in muscle mass[34]. Given that studies suggest frailty is associated with increased healthcare costs, independent of socio-demographics and comorbidity, identifying populations that could most benefit from interventions to reduce frailty could have significant public health impact[28]. With regard to frailty prevention, this project gives weight to the recent body of literature suggesting that reported cigarette smoking exposure may play a causal role in the development of frailty. This project also suggests that the intensity and duration of smoking exposure could play a more pivotal role in frailty development, rather than current smoking exposure alone. Future studies are needed to determine the long-term impacts of various levels of

smoking exposure on frailty risk and smoking interventions to reduce frailty risk among women with and without HIV infection.

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